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Sahli's Tuberculin Treatment

INCLUDING A DISCUSSION OF THE

Nature and Action of Tuberculin and of
Immunity to Tuberculosis

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BY

DR. HERMANN SAHLI,

*Professor of Medicine in the University of Berne ;
Director of the Medical Clinic.*

Translated from the third German Edition by

WILFRED B. CHRISTOPHERSON,

With an Introductory Note by

EGBERT MORLAND, M.B. and B.Sc.Lond., M.D.Berne.

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Tuberculin in Diagnosis and Treatment

by Drs. BANDELIER and ROEPKE. Translated from the German by E. C. MORLAND, M.B. With coloured Illustration and Charts. 7/6 net. Postage 6d.

The Ophthalmic and Cutaneous Diagnosis of Tuberculosis

by Dr. WOLFF EISNER. With introductory note by C. THEODORE WILLIAMS, M.D. Translated from the German. With many Illustrations, 2 coloured and 11 folding charts. 7/6 net. Postage 6d.

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AUTHOR'S PREFACE.

TUBERCULIN treatment was inaugurated by Koch in the 'nineties, and it seemed as though it was destined to oblivion for the medical world in consequence of numerous disasters, but, after many years, it has recently been resuscitated in the form of a reactionless treatment and is beginning to give satisfactory results in the hands of many a skilful practitioner. But for the clinician who wishes to take up tuberculin treatment, neither is the phrase "reactionless treatment" in itself a complete guide to technique, nor does the mere principle afford any help in the selection of cases and in that proper appreciation of success and failure which is essential for the improvement of results. In every department of therapy, the practitioner who turns his knowledge to the best practical account is not the one who employs remedies by rule of thumb, but who, with reason and senses trained to the observation of Nature's workshop, knows exactly what he does and what he has to expect. This is doubly true of tuberculin treatment, for here the conditions are so complicated that the good often lies but a hair's breadth from the bad. Herein lies the application of the motto on the title-page of this book.

The recent increase in the employment of tuberculin led me, about a year and a half ago, to present to the medical public a careful and critical analysis summarizing our knowledge of the action of tuberculin, and the intimately connected problems of cure and immunity in tuberculosis. This took the form of a third enlarged

edition of a work which previously appeared in the *Correspondenzblatt für Schweizer Aerzte*. For it has been impressed upon me that the especial need of many practitioners is a sufficiently intimate knowledge of the complicated factors concerned in the cure of tuberculosis and the action of tuberculin, as they so often assume that these are simple immunizing actions. From such a shallow study there results not only bad choice of cases for tuberculin treatment and faulty technique, but also a lack of accuracy in judging the results. This lack of judgment can never be supplied by statistics and leads to aimless and unscientific experimenting with all possible kinds of tuberculin, resulting only in false conclusions.

In my attempt here to outline a rational basis and scheme for the modern tuberculin treatment, which I regard as one of the most important problems of therapy and a great advance in the modern campaign against tuberculosis, I have been fortunate in securing for the translation the able assistance of Dr. Morland and Mr. Christopherson, who have undertaken the difficult task of translating complicated trains of thought with no little ability and devotion. I have myself looked through the proof of the English text and tender them my sincere thanks for the skilful way in which they have accomplished the task.

I trust, then, that this English translation of my work may help to pave the way for a better understanding of a truly rational tuberculin treatment by doing away with the hard-and-fast routine which still rules in many places and to incite its opponents to that study of the question which it deserves.

Berne,

HERMANN SAHLI.

February 5, 1912.

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INTRODUCTORY NOTE.

THIS monograph by Sahli emanates from the Clinic at Berne which, even in greater measure than Switzerland generally, is cosmopolitan in its views and outlook. The work may be taken as typical of the best methods of the Berne School, based as it is on original observations carried out in the Clinic over a period of years previous to publication—work comparable with that of Kocher or Langhans in the sister faculties of surgery and Pathology.

For reasons which Professor Sahli emphasizes in the text the book deals almost exclusively with tuberculin produced by Professor Beraneck at Neuchâtel; but the principles enunciated are of general application and there is nothing to prevent the book being taken as a guide to the administration of any kind of tuberculin.

Tuberculin Beraneck was introduced into British practice by Dr. R. W. Philip of Edinburgh, who employs a series of dilutions on a decimal scale which thus differs from Sahli's series of dilutions where each is but twice as strong as the preceding letter. The table on the following page gives the relation between these two scales, which coincide exactly at one point only—Sahli's C being identical with Philip's TBk₂; and approximately at a second useful point—A/256 being practically identical with TBk₅.*

The translation has been done for me by my laboratory assistant, Mr. W. B. Christopherson, from the third

* The agent for Professor Beraneck's tuberculin in Great Britain is Mr. A. K. Stewart, Lynedoch Place, Edinburgh, from whom the various dilutions, according to either scale, may be obtained.

enlarged German edition of "Tuberkulinbehandlung und Tuberkuloseimmunität" (Benno Schwabe and Co., Basel, 1910). Professor Sahli has made alterations and additions bringing the work up to date, and has also written a new preface for the English edition.

Arosa, Switzerland.

EGBERT MORLAND.

March, 1912.

TABLE OF EQUIVALENT DILUTIONS OF TUBERCULIN BERANECK.

1 c.c. of T Bk on Sahli's scale	Is equivalent on Philip's scale to	1 c.c. of T Bk on Philip's scale	Is equivalent on Sahli's scale to
H ..	T Bk ₁ 3·20 c.c.	T Bk ₁ ..	G .62 c.c.
G ..	T Bk ₁ 1·60	T Bk ₂ ..	C 1·00
F ..	T Bk ₁ .80	T Bk ₃ ..	A/2 .80
E ..	T Bk ₁ .40	T Bk ₄ ..	A/16 .64
D ..	T Bk ₁ .20	T Bk ₅ ..	A/256 1·00
C ..	T Bk 1·00	T Bk ₆ ..	A/1024 .40
B ..	T Bk ₂ .50		
A ..	T Bk ₂ .25		
A/2 ..	T Bk ₂ .12		
A/4 ..	T Bk ₃ .62		
A/8 ..	T Bk ₃ .31		
A/16 ..	T Bk ₃ .16		
A/32 ..	T Bk ₄ .78		
A/64 ..	T Bk ₄ .39		
A/128 ..	T Bk ₄ .20		
A/256 ..	T Bk ₅ 1·00		
A/512 ..	T Bk ₅ .50		
A/1024 ..	T Bk .25		

SAHLI'S TUBERCULIN TREATMENT.

"Eritis sicut deus scientes bonum et malum."

I.—PRACTICAL PART.

INTRODUCTION.

EVER since the first announcements of Koch, the tuberculin question has remained in the balance. On the one side we have strong opponents of all tuberculin treatment who take up the same position to-day as one did of necessity in the nineties, when, owing to an erroneous theory and incorrect practice of tuberculin treatment, a period of the most bitter disappointment followed the initial outburst of enthusiasm. On the other side we find tuberculin therapists who, in their optimism, go much too far and do not realize that in addition to the cases they treat successfully, often, indeed, strongly influenced by auto-suggestion, in many others they are doing harm by the treatment. Opinions are, in this way, still unsettled, but for him who has followed the question and has himself been through the various phases of tuberculin treatment, there is such a store of facts and experience, that it does not seem a difficult matter to form a judgment on the clinical questions that arise, to define exactly the value of tuberculin therapy, and, what is in practice the most important, to decide on a method which shall remove from tuberculin treatment its indisputably two-edged character.

**Conflicting
Estimates of
the Value of
Tuberculin
Treatment.**

Requests have reached me from many quarters for my views on and experiences of tuberculin treatment, since the necessity is ever increasing for the practitioner to look into the question.

Reasons for Writing. As I have been working for more than ten years on the theory and practice of this subject, I feel obliged to accede to the request, especially as I am convinced that tuberculin treatment is not always carried out on correct principles, and thus the patient is frequently rather harmed than benefited. On this fact depend the striking differences of opinion of the value of tuberculin treatment.

Mistakes in the employment of tuberculin arise largely from the fact that for the doctor who has not the opportunity to follow up all the rich literature of experimental therapy in infectious diseases, it is hardly possible to find time to study all the theories of present-day literature, sometimes mutually contradictory, and often going beyond the facts : for it is unfortunately more and more evident that the various writers move only in their narrow circles without working from comprehensive clinical standpoints, and do not attempt to put together into one picture the multitude of their experiences.*

The practitioner, then, chiefly suffers from the fact that medical research is becoming more and more divided into work of perplexing detail, which is only of value when its results are simplified and abridged and are considered from broader standpoints.

* Simple phagocytosis with or without opsonin is held by some to be the essential point in the cure of infectious diseases ; others put all their trust in bactericidal actions, others in antitoxic actions and so on. One often fails to realize with what wonderful precision the various functions of the organism are balanced and adjusted to each other, and how full is the organic world of complicated combinations of actions, all heedless of the resulting difficulties of comprehension.

GENERAL PRINCIPLES.

The tuberculins I have used are Koch's new and old, Denys', and of late chiefly Beraneck's. With the last of these, I have recently treated some hundreds of cases in hospital and in private practice. Though, of course, there are wide differences between the various tuberculins, yet there is no doubt that in all the therapeutic principle is the same. A more detailed confirmation of this statement is postponed to the second (theoretical) part of this book. At any rate, experience shows that good or bad results may follow the use of any of the ordinary tuberculins, according to the method of treatment employed. The principles of treatment by tuberculin, then, which are outlined in the following pages, hold *mutatis mutandis* for all tuberculins. Beraneck's tuberculin is chosen for discussion as it appears to be, theoretically and practically, the best based, and further because it is very little known, having but lately been supplied for general use; it is to be obtained from Professor Beraneck's Bacteriological Laboratory at Neuchâtel, Switzerland, and also in this country (c.f. Translator's Preface).

From the particulars published by Beraneck,¹ it seems that this preparation contains the specific immunizing toxins of a tubercle-culture from both the broth and the bacillary bodies; that these products are, as far as possible, original and unaltered and with the least admixture of other toxic substances, arising from the culture-

**Various
Tuberculins.**

**Beraneck's
Tuberculin.**

medium (peptone, &c.), and which unnecessarily raise the toxicity of many tuberculins without increasing their power of immunization. It is not necessary, at this stage, to discuss the properties peculiar to Beraneck's tuberculin; it is fully described in the second section of the book; further information is found in Beraneck's treatise.

Although striking cures are obtained with all tuberculins, it is nevertheless necessary, in order to use them correctly, that it be clearly understood that

**Tuberculin
not a True
Specific.**

they possess no direct healing power, no antidote other than tubercle-toxin. The application of tuberculin is, then, different in principle from that of a true specific; for instance, there can be no resemblance between tuberculin treatment and the serum treatment of diphtheria; it is owing to such mental confusion, which is evident in faulty methods of practice, that tuberculin treatment which, when carried out on correct principles, is one of the greatest advances in modern therapeutics, has been to some extent discredited.

We shall not get a proper understanding of tuberculin treatment without first explaining the sense in which tuberculin is the toxin of tuberculosis (*cf.* Theoretical Part). To show the necessity of making a more exact study of the toxic nature of tuberculin, I need only point to the striking fact brought to light by recent investigations, that healthy animals can tolerate such large doses of tuberculin* that one might easily make a false estimate of the toxic nature of these substances if it were not

* For example, a healthy guinea-pig tolerates 1 to 2 grm. of Koch's old tuberculin, and over 10 c.c. of concentrated tuberculin Beraneck, 62½ times stronger than the strongest solution (H) of this preparation used for treatment.

known that the very smallest doses can produce marked toxic phenomena in the tuberculous man and animal.

The action of tuberculin depends upon what I have called an actively immunizing curative process, in other words upon the activity of those processes,

**Action of
Tuberculin and
Tox-immunity.** initiated by the toxin of the disease, by which the organism can protect itself against infections. It depends, then, on the arousing of true natural healing processes, the mechanism of which is to be explained in the Theoretical Part.

We can, however, here anticipate that one of the most important factors of these natural healing processes of the tuberculin consists of a gradual insensibilization of the organism to the chemical tubercle-toxin, a tox-immunity obtained by assimilation of gradually rising doses of tuberculin.

A tradition of the Pontic King Mithridates comes down from antiquity that he, in his fear of all kinds of poison, sought to render himself insensitive to them by consuming increasing doses of them. He attained this end to such an extent that when in his conflicts with Pompey, despairing of his fate, he sought to poison himself and his whole family, he failed and was stabbed at his own wish by his bodyguard. The expression "mithridatism" is used, therefore, as a general designation of all possible forms of tox-immunity by progressive assimilation of toxin. It has, of course, now been shown that very different processes take part in this tox-immunity according to the nature of the toxin in question. It is thus an established fact that the long-known insensibility to arsenic taken internally is caused by the decreasing quantities of the drug which are absorbed by the gut; the insensibility to morphia depends on the increasing power of the organism, especially of the liver, to destroy the poison. On the contrary, the tox-immunity to bacterial toxins (called toxic immunity or toxic immunization) depends chiefly on the action of antibodies in the neutralization of the chemical affinities of the toxins. The special nature of this tox-immunity in tuberculosis, and the part it plays in the therapeutic action of tuberculin will receive detailed treatment in the theoretical section; the conditions here are rather complicated.

The fact that such a tox-immunity to tuberculin is

possible to a very high degree not only in the healthy but also in the tuberculous, is evident since the tolerance of tuberculin in the tuberculous can be raised a million times by gradual increase of dose. The second part of this book gives the theoretical explanation of this tox-immunity and the proof that the actions of tuberculin are, in principle, identical with the toxic actions of natural tuberculosis, a proof of fundamental necessity for tuberculin treatment.

This immunizing process is analogous to the natural process of hardening in which, as in many other cases,

it is a question of raising a natural capacity present in the organism of reacting to the tubercular toxin. Such reactions are clearly in the end only of a chemical antitoxic nature ; but these antitoxic actions are of quite a different kind from those on which the serum treatment of diphtheria and tetanus are based. By means of such increasing reactions, the body succeeds not only in tolerating increased quantities of the tuberculin injected but also in rendering innocuous the toxins produced in the tubercular foci.

It must not be thought, however, that tuberculin treatment is only directed to tox-immunity ; for such a tox-

immunity to the tubercular toxin is, as will be explained in the theoretical part, impossible without certain irritative actions or reactive processes of the toxin, partly general, partly localized in the foci ; these irritative actions are also of importance for tuberculin treatment.

To get a clear idea of these irritative actions and of the whole clinical conception of the working of tuberculin, I will trespass somewhat on the theoretical section : according to the doctrine of Wolff-Eisner,²

which I consider correct, tuberculin (which, as we shall see, is essentially the protein of tubercle-bacilli or tubercle-endotoxin, *i.e.*, the toxic body-substance of tubercle-bacilli) calls forth the formation of a bacteriotropic antibody, just as do the tubercle-bacilli themselves. By analogy with bacteriolysin, Wolff-Eisner calls this antibody, identical with the Wassermann-Bruck anti-tuberculin, a lysin, implying, of course, a tuberculinolysin; he assumes that just as bacilli are destroyed by a bacteriolysin, so the bacterial protein of the tuberculin is split up and chemically changed by the action of the tuberculinolysin.

The toxic action of the tuberculin, however, is not annulled by this means as by an antitoxin; on the contrary, Wolff-Eisner shows, on good grounds, that only by means of this tuberculinolysin is the real, active tubercle-toxin produced, in the form of *lysinized tuberculin*, which is far more toxic than the genuine original tuberculin, just as albumoses and peptones are more toxic than primary albumin. These secondarily formed toxic substances are those which, in the natural course of tuberculosis, cause in the tubercular foci the well-known inflammatory irritative actions of the tuberculous infection, since in this case the tubercle-bacilli are dissolved up by the lysin just as in the focal or local reactions of tuberculin. After an injection of tuberculin, the reactive irritative actions are probably produced (Theoretical Part, p. 133) because, by the active lysin in a tuberculous organism, the tuberculin becomes a toxic substance causing the irritation of the inflamed foci. The general actions of the lysinized tuberculin (arising from the foci or from the injected tuberculin, by the action of lysin) are chiefly characterized by febrile phenomena which, if of spontaneous

The
Intermediate
Step.

origin, are called tubercular intoxication, if a result of artificial tuberculin injection, general tuberculin reactions.

It must now be assumed that the organism reacts by the formation of antitoxic antibodies to the local and general action of the tuberculin which has been lysinized and is therefore toxic.

According to this idea, then, the increase of toxicity of the tuberculin by the action of lysin is the intermediate step in the ultimate "detoxication" of the lysinized tuberculin by antitoxin.

The existence of these antitoxic bodies is difficult to prove directly, as will be shown in the theoretical part; but apart from the fact that certain attempts at proof have been successful, their existence is a necessary postulate for the explanation of the healing action of tuberculin and the possibility of an increasing tolerance to increasing doses of tuberculin.

The antibodies of tuberculosis of which we shall speak are, then, of two kinds: (1) *The primary lytic antibodies*, with which the tuberculin and tubercle-bacilli combine to form toxic decomposition products, by means of which we must assume that the tubercle-bacilli are, if not at once destroyed, at least weakened; these decomposition products cause the general and localized irritative actions. (2) *The secondary antitoxic antibodies* which act against the toxic actions of the lysinized tuberculin and the lysinized tubercle-bacilli.

We shall see that great importance is to be attached not only to the secondary specific antitoxic actions but also to local irritative actions caused by the lysinized tuberculin, since these latter render active the non-specific curative forces of the organism: these are, for instance, the in-

**The Anti-
bodies of
Tuberculosis.**

**The Natural
Curative
Factors.**

flammatory hyperæmia and exudation, the circumvallation of the leucocytes, by which Bartel and Neumann³ have shown that the tubercle-bacilli are weakened, perhaps also the caseation which occurs depriving the tubercle-bacilli of nourishment. All these healing forces are to a certain extent present in the natural course of tuberculosis, but they can be increased by tuberculin injections.

In a word, the increase of tox-immunity or the specific antitoxic efforts of the organism, and the stimulation of the local processes of physiological defence in the tubercular foci, is the essence of tuberculin treatment.

This statement will be further explained in the Theoretical Part. Here I merely want to show that tuberculin action is not only tox-immunity; besides the secondary specific antitoxic actions described, on which the tox-immunity depends, I want to emphasize the importance of the incitement of the natural healing processes caused by the tuberculin and of the irritative actions promoted by lysin; all these are needed for the explanation of the therapeutic action of tuberculin.*

With regard to these irritative actions, experience shows that in tuberculin treatment if they are not to be a source of danger, they must be as far as possible clinically imperceptible. For, in the *unfavourable* course of tuberculosis, these same irritative actions are the cause of tissue damage, since they exceed the optimum amount, thus aiding the progression of the disease and even in the *favourable* therapeutic irritative action of tuberculin the important factor is always the tissue-damage. In treatment, by regulating the dose, this should be so

**Reactions
should be
clinically
imperceptible.**

* I must mention here that in addition to the lysin theory, a histogenous explanation of the irritative actions of tuberculin is also possible. (Cf. pp. 141-143 of the Theoretical Part.)

slight as to render the anti-action to the advantage of the organism; for if it proves too strong, it can only promote its destruction. Therefore, even if not all clinically perceptible tuberculin reactions, which, since the time of Koch's discoveries, have shown themselves in febrile phenomena and extension of inflammation in the tubercular foci, are necessarily dangerous, clinical observation has nevertheless definitely proved that from the time when those clinically manifest signs of reaction occur in tuberculin treatment it becomes two-edged and its action uncontrollable, since the organism is not always able to compensate the tissue-damage at the root of the reactions. It cannot therefore be sufficiently emphasized that a tuberculin treatment which seeks to do more than exert quite a gradual influence on the rousing to action of the two healing processes in the natural recovery from tuberculosis, is two-edged. The attempt, in tuberculin treatment, to force the cure in a so-to-speak heroic manner by the production of reactions such as the raising of fever and the incitement of local inflammatory phenomena, may, indeed, be occasionally successful, but is never under control and always a source of danger.

The tendency in tuberculin treatment of restraining by careful dosage, and as far as possible avoiding reactions, has made itself felt in the tuberculin literature of the last few years. As far as I know, the possibilities of a reactionless tuberculin treatment were first pointed out by Lichtheim⁴ and it was first practised by Götsch,⁵ who has thereby done very real service to tuberculin treatment. The claims of the treatment were then confirmed by Denys⁶ and Schnöller.⁷ My own clinical experiences, previous to and independent of the informa-

**Pioneers of
Reactionless
Method.**

tion of Götsch, Denys and Schnöller, had convinced me of the value of a tuberculin treatment as far as possible reactionless, but my experiences were not published until the first edition of this book (1906).

In a book published early in 1891, Lichtheim makes the following statement: "On account of these observations, I consider it expedient to avoid as completely as possible all signs of reactions in the phthisical." He was thus the first to recommend without reserve the avoidance of reactions, a measure quite contradictory to the prevailing views and the Koch scheme of tuberculin treatment. In a publication of slightly later date, he certainly wavered somewhat in his views and in a certain measure withdrew from his former position, for he says that to make quicker progress in the cure, actual febrile reactions should be produced from time to time. Soon after this, the general disappointment caused the majority of doctors to give up tuberculin treatment, so that the observations of Lichtheim were practically lost. This does not, however, alter the fact that Lichtheim was the first to conceive the possibility of a reactionless tuberculin treatment, and I take this opportunity of showing his priority in this respect.

It is to be hoped that friends will be won for a mild form of tuberculin treatment by the arguments used in this treatise, the chief aim of which is to establish the method on a rational basis and to disprove the assertion that more can be done by a treatment in which reactions are intentionally produced, as is still the practice in many quarters and has even been recommended by Koch for his latest tuberculin.

The aim of tuberculin treatment is, then, the stimulation of the natural healing forces which play the decisive part in the spontaneous cure of tuberculosis, a spontaneous cure which Nägeli and Burckhardt⁸ have shown to be so frequent; these are (1) the progressive production of a general tox-immunity and (2) the stimulation of the local healing forces in the tubercular foci. The question at once arises why, in certain cases that come up for treatment,

**The aim of
Tuberculin
Treatment.**

the organism does not of itself attain this tox-immunity to the tubercular toxin, does not contain in its foci the spontaneous incitement to healing, and what advantages artificial tuberculinization can offer over natural tuberculinization in such cases? Two essential circumstances bear on the seemingly paradoxical fact that such advantages do exist and create more favourable conditions for a tox-immunity due to tuberculin injections; these are:—(1) That by subcutaneous injection only a small part of the toxin goes to damage the tubercular foci, the larger proportion being rendered innocuous in the healthy organs and causing the production of antibodies: in the natural course of tuberculosis, the toxin has mainly a local, harmful action without displaying a sufficient general healing action; and (2) that in the natural course of tuberculosis, especially of early cases, the toxin production is so gradual that the irritative action causing the formation both of the primary lytic and of the secondary antitoxic antibodies may easily prove less than that afforded by subcutaneous injection, when the tuberculin is at once diffused into general circulation.

Thus, by tuberculin treatment, not only the antitoxic forces of the organism are increased but also the lytic actions at work in the foci; these both weaken the tubercle-bacilli, and also incite the local healing forces by local toxic action.

Its Results.

It is quite conceivable that in the natural course of tuberculosis, especially in early cases which are the special object of tuberculin treatment, these two influences come insufficiently into play. Further, in comparing artificial tuberculinization by isolated doses of the toxin with the continuous natural tuberculin action of natural tuberculosis, it will at once be realized that the temporary tuberculin actions naturally do not do the same

damage as the lasting influence of the same or even a smaller amount of toxin.

Tuberculin action, then, in addition to tox-immunity, includes other natural healing processes, which must be brought about by the organism itself (*cf.* **Unsuitable Cases.** p. 15); tuberculin treatment will prove of no use in cases where the organism is incapable of doing this, whether tox-immunity has been obtained or not.

The effect of tuberculin treatment is, as I have said, an *immunizing healing action*, which takes place according to the general principles of immunization; but this action must be very clearly distinguished from a real and complete immunization. All attempts that have been made to secure complete immunity in man or beast against living tubercle-bacilli by means of dead tubercle-toxins have proved a failure, the reasons for which are given in the theoretical part. Therefore, in tuberculin treatment it is always a question of attaining only a relative immunity. This consists of an increased capacity for resistance by the stimulation of those physiological and anatomical processes by means of which tuberculosis so often heals spontaneously; thus, Nägeli and Burckhardt (*loc. cit.*) have shown, in their anatomical research, that nearly every adult has had a tuberculous infection.

The experience is often met with in tuberculin treatment, that although it has succeeded in rendering the patient insensible to the largest doses of tuberculin, and generally in checking the tuberculous process, it is often unable to arrest it entirely; this exactly agrees with the distinction we have made between the immunizing healing action of tuberculin treatment and a real immunization,

and with the fact that so far no immunization of animals by chemical tubercle-toxin has proved successful. This is very different from the ordinary conditions for immunization, well-illustrated in diphtheria, when an infection is completely cured when the organism possesses a high tox-immunity or a large amount of antibodies. The condition for the cure of tuberculosis by immunization is not merely that of a general tox-immunity to tuberculin; the antibodies produced by the treatment are certainly present at the site of the tuberculous disease, but the avascularity of the foci prevents their penetration in sufficient concentration to the heart of the tuberculous tissue; they are thus prevented from displaying their protective action. The presence of the tubercle-toxin in the foci in a very high degree of concentration further helps to make the problem a very difficult one. A parallel to this last factor is found in the fact that even quite large doses of ordinary diphtheria-antitoxin are not able to counteract the effect of the local inflammatory action of injections of strong diphtheria-toxin (quoted from Wolff-Eisner, *loc. cit.* p. 237). So in the standardization of a diphtheria-serum by its action on the local inflammation caused by diphtheria-toxin, the serum must be injected at the same place as the toxin. A further analogy is to be seen in the experience that diphtheria-toxin produces cutaneous reactions in children suffering from diphtheria even after previous injection of three to five thousand units of antitoxin; the general action is not sufficient to neutralize the toxin at work locally in high concentration. In addition to the difficulties caused by the high concentration of the tubercle-toxin in the foci, there is yet another; the micro-organisms, as in all infectious diseases, are able so to adapt themselves to the

**Special
Difficulties of
Tuberculin
Treatment.**

organism that they resist all its opposing forces. These points are very clearly illustrated by the atoxyl treatment of animals suffering from trypanosome infections; by means of atoxyl, the course of the disease is certainly favourably influenced and a cure is often effected; but, in spite of the clinical improvement or cure, the remaining trypanosomes almost always show a certain hereditary atoxyl tolerance and can no longer be influenced by it. It can, then, be easily understood that even a high degree of tox-immunity does not constitute a cure of the particular case. Conversely, human tuberculosis can heal when reactions are produced by the very smallest doses of tuberculin, a circumstance which proves the entire absence of any general tox-immunity. This proves that in tuberculosis, besides general tox-immunity and a general factor of immunity, there are other factors which promote a cure.*

The other necessary factors are only of a local nature, connected with the foci themselves. An objection might be raised to this idea that the local tuberculous processes are in the end only to be explained by local toxic actions, and this the more since tubercles can be produced by dead tubercle-bacilli and even by tuberculin itself, in the cutaneous and conjunctival reactions (*cf.* p. 113). It might be said, then, that in the cases where tuberculosis is cured in spite of a persistent tuberculin sensitiveness, it is the local tox-immunity in the seat of disease that promotes the cure. These arguments may be

* This explains the fact, which can to-day hardly be disputed, that by the diagnostic employment of tuberculin in all its forms, it is impossible to distinguish between healed and unhealed tuberculosis.

logically correct, but they cannot get over the fact that it is not possible to immunize against living tubercle-bacilli by chemical tubercle-toxins; even if some new technique made this possible, the clinical facts of the cure of tuberculosis would still be right, that even a high degree of tuberculin immunity (insensitiveness to the largest doses of tuberculin) does not necessarily cure the tuberculous process and that tuberculosis can be cured without general tuberculin immunity. It must be granted, then, that the local tox-immunity, if this designation may be given to the cause of healing, is quite a different thing from the general tox-immunity.

The healing of tuberculosis is, then, independent of general tubercle tox-immunity; this is only to be explained by assuming that local neutralization of the toxin of living tubercle-bacilli is attained by other means than the general tox-immunity, which merely assists the process but is not the direct cause of it. The means the organism has at its disposal for the local detoxication of the tubercular foci are not far to seek. They consist of the non-specific means mentioned on pp. 8-9, which are contained in the inflammatory process. One need not be an adherent of the phagocytic school in its original, uncompromising form, to realize how many useful factors are provided by inflammation. The most active are the rich currents of blood and lymph in the inflamed part, the action of complement contained in the inflammatory exudate and the accumulation of cellular material in the form of leucocytes, blood-platelets and lymphocytes. With the aid of these forces, the tubercle-toxin is rendered innocuous by a purely local process; this consists of two parts:—

- (1) There are, in the tubercular foci, large quantities

of material with unsaturated affinities such as the albuminoid bodies of the blood, lymph and exudates and the cell-substance of leucocytes and lymphocytes. These, so to speak, neutralize the local toxin and the leucocytes, even when they do not phagocyte, act as food for powder.

Their Twofold Action.

A section from a human streptococcal pneumonia recently supplied me with a proof of this power of absorbing toxin possessed by leucocytes. The exudate was filled with extraordinarily copious colonies of streptococci lying chiefly in the leucocytes and pulmonary alveolar epithelium. In many places the cell-substance along the chains of streptococci had lost its power of taking the stain, so that they appeared embedded in strips of clearly necrotic protoplasm. This could only be explained by assuming a local toxic action of the streptococci on the cell-substance, which is evidently identical with a partial neutralization of the toxin by the cellular protoplasm. There is no question of phagocytosis in the teleological sense of Metschnikoff, since all the cells, including those of the lung tissue, were indiscriminately filled with streptococci which had clearly grown into them. Denys proved some time ago that streptococci produce a leucocytic toxin, the so-called leucocidin; this again speaks strongly for the fact that leucocytes possess a toxin-absorbing power, perhaps just as important a function as that of phagocytosis.

(2) Bartel and Neumann (*loc. cit.*) have shown that the lymphocytes possess a direct weakening power over the tubercle-bacilli.

By these means the local damage is so much reduced in favourable cases that the tubercle-bacilli can be broken down as if they were saprophytes by the metabolism of the tissues. Then there are the ferment actions of the leucocytes, increased oxidation resulting from an increased blood-supply, inclosure of the foci in connective tissue, caseation depriving the tubercle-bacilli of nourishment and many other factors; so that there is, indeed, an abundance of local healing forces even if the decisive value of true phagocytosis be doubted.

**Ferment
Action of
Leucocytes.**

In addition to their oxidizing action, the leucocytes possess a most important ferment action, a tryptic action discovered by Müller, Kolaczek and Jochmann, though, strangely enough, Müller and Peisner^o consider this detrimental to the course of an inflammatory process. They hold that the tryptic leucocyte ferment, collecting in large quantities during suppuration, melts away the tissues and aids the progress of the suppuration. Starting from this standpoint, the writers have founded and tested a so-called anti-ferment treatment of suppurative processes. Normal blood serum contains an anti-ferment of this leucocyte ferment; the treatment consists in the injection of the normal serum with a view to restraining the suppuration. It is asserted that favourable results have thereby been obtained, suppuration having been quickly dried up and the tissue-destruction reduced to a minimum. When one considers the extraordinary adaptability of the animal organism, it does not seem possible that the tryptic ferment of the leucocytes, otherwise of very real value, can have such a defect. If then, as I do not doubt, the tryptic ferment does cause tissue-destruction, is it not probable that in the severe infections, where so large a quantity of leucocytes is produced, this destruction is really advantageous to the organism, as the discharge from the abscess formed totally eliminates the harmful elements? I admit that such a useful arrangement may overshoot the mark, examples of which are frequent in pathology. Reflex muscle contractions are very useful as a means of defence against injury, but bones can be broken in this way. But is it not probable that only those parts of the tissues are destroyed by the tryptic action of leucocytes which are already doomed to necrotic destruction by the action of bacteria? The favourable action of the anti-ferment serum injected may not depend on its anti-ferment content; it may simply be equivalent to the injection of normal serum into the inflamed tissues, bringing to the point of action what I have called inflammatory antibodies which help to neutralize the toxin. Such antibodies are, indeed, supplied in the exudation fluid, but perhaps in insufficient quantity. May not, then, this so-called anti-ferment treatment be merely a kind of serum treatment with normal serum, analogous to that which I have recommended for therapeutic trial in general infections in the form of subcutaneous injections of large quantities of normal human serum? A suggested method of treatment is found in the *Corres-Blatt für Schweizer Ärzte*, No. 20, 1909.

If it be objected that the ferment must also serve some useful purpose, I naturally agree, but must point out that this could not be if, in the inflammatory process, the ferment and anti-ferment simply neutralized each other. In this case, Nature would have dropped the proteolytic ferment. The anti-ferment action is clearly not directed to the process of inflammation but to the circulating blood where, indeed, the tryptic action of the leucocytes must be suppressed

in the interests of the organism, since no useful end can be served by an auto-digestion of the blood.

The chemical toxin-binding substances formed in the process of inflammation might be called inflammatory antibodies; but these differ from antibodies in the ordinary sense of the word since they are not necessarily specific and do not merely arise from the process of immunization, but are present also in the healthy non-immunized body. The relation between the neutralization of tubercle-toxin by these substances in the tubercle foci, and a true antitoxic neutralization of tuberculin in immunization, is comparable to that between Wassermann's neutralization of tetanus-toxin by triturated nerve-substance, and by real tetanus-antitoxin produced in immunization. The local healing forces that have been mentioned are sufficient, without general tox-immunity, to cure a local tubercular focus. If the organism is denied these healing forces by reason of some weakness of constitution, it is clear that not even the strongest general tox-immunity can free it from the local toxic actions caused by the immediate contact of the bacilli. The local concentration of toxin is so high that the violence of its action is a million times greater than any general toxic action.

Apart from the evidence given on p. 17, and the production of leucocidin by staphylococci, the existence of these inflammatory antibodies is proved by the experiments of M. Gruber and Kenzo Futaki.¹⁰ They found that leucocytes and even blood-platelets form anthracocidal substances ("leucanthrocidin" and "placanthrocidin") which without phagocytosis exert a powerful extracellular action on anthrax-bacilli, completely destroying them. Whether this is a purely specific action

**Inflammatory
Antibodies.**

**Proofs of their
Existence.**

on anthrax-bacilli, or a more general one, the authors do not state; they maintain, however, that these substances are distinct from serum-alexin. The action of injections of collargol in infections is often explained by the setting free of protective bodies by the destruction of leucocytes,¹¹ and these are clearly analogous to the inflammatory antibodies I have suggested.

It is further very probable that in infections, the leucocytes, acted upon by the antigen, also form specific antibodies. Pfeiffer and Marx and Wassermann have shown that immune bodies of the leucocytes originate chiefly from the bone-marrow; it can, therefore, almost be taken for granted that the leucocytes, as travelling representatives, so to speak, of the bone-marrow, still continue to supply such specific antibodies after their emigration from it. This view agrees with the researches of Metschnikoff¹² who ascribed the origin of antibodies in large measure to the breaking down of phagocytic elements. Petterson and von Salimbéni,¹³ too, found that the injection into the peritoneum of washed leucocytes of animals immunized against the vibrio of Metschnikoff, could protect other animals from infection by the vibrio, and this not by phagocytosis, but by a bactericidal action of a purely chemical nature during the disintegration of the leucocytes.

We come to the conclusion, then, that in the healing of local tubercular foci, certain antibodies play a part; these are not all specific or immunizing in the real sense of the words; some have perhaps a certain immunizing action, but are formed and act locally. These will all be included under the general term "inflammatory antibodies." In view of what has been said about the

**Tuberculin
Treatment
increases the
Inflammatory
Antibodies.**

mechanism of tuberculin action, it must be assumed that these factors also can be increased by means of the irritative conditions produced by tuberculin treatment, and to this fact is very largely due the efficiency of the treatment.

The very fact that large doses of tuberculin produce not only febrile reactions, but the local inflammatory phenomena known as focal or local reactions, shows that by tuberculin treatment the local irritative actions are increased, and with them the local forces of physiological defence. We have seen, however, that as soon as this irritation reaches a point at which it is clinically manifest, it is two-edged and dangerous; for these changes in the foci caused by such local reactions are characterized by an aggravation of the condition, both at the time and often as a lasting result. It is true that this aggravation may in the end be in favour of the organism on account of the physiological anti-actions which accompany it, for the local reaction itself has a healing action. The balance may, however, be on the wrong side, resulting in a decreased defensive power of the tissues, and an aggravation of the disease in the tubercular foci.

For this reason, the view is increasingly gaining ground that the production of local inflammatory reactions by tuberculin is risky and uncertain, and I am convinced that it is far wiser to avoid as far as possible all such local reactions by a careful regulation of the tuberculin dose. The term "tuberculin reaction" has lost the optimistic significance it had at the time of Koch's method of treatment, when the inflammatory phenomena in the foci were considered the sole factor for cure. The term "reaction" for these clinical phenomena is to-day only justified in the sense of a chemical reaction. It is very uncertain

**Local
Inflammatory
Reactions must
be avoided,**

whether such a reaction is also a reaction in the biological sense of the word as generally used in medicine, a successful opposing force to the damage done by the toxin; the word should not, therefore, be used with this entirely favourable significance in tuberculin treatment. It would be much better to drop the word altogether, and substitute the term "local toxic action" or "increased toxic inflammation." This seems hardly possible, however, as the word "reaction" has become so thoroughly naturalized in the terminology of tuberculin treatment.

These remarks apply also to the febrile and other phenomena usually accompanying local reactions which are so often optimistically described by the term "general reactions," which does not convey a correct idea of their true significance. They, too, must be avoided, since they are generally the expression of at least a temporary aggravation in foci which otherwise only give rise to fever when the patient is not doing well. In tuberculin treatment, focal reactions often take place without any general reactions and similarly general reactions without focal reactions. General reactions are, of course, caused by the general toxic action of the lysinized tuberculin, and the question must therefore be decided as to whether the causation of fever in itself serves any useful purpose. A useful purpose was once ascribed to a reactive treatment of this kind since it was thought that the fever of infectious diseases was in itself a healing factor. The organism responds to so many, indeed to nearly all infections, with fever, and the capacity for fever is seen throughout its phylogenetic development. These two facts have led many to see a useful agent in fever itself.

This assumption, however, is corroborated by a section only of the experimental research into the value or

danger of fever. Rolly and Meltzer¹⁴ quote results which show a larger production of antibodies and increased phagocytosis in overheated animals, as do also the results of Lüdke's¹⁵ research : Lemaire,¹⁶ on the other hand, maintains that the production of antibodies in dogs infected with *Bacillus coli* is not unfavourably influenced by the cessation of fever. The experiments of Barankeieff¹⁷ show that infections are unfavourably influenced by febrile conditions : further, Wright, in his work on the opsonic index, has discovered that the so-called negative phase of immunity after tuberculin injection can last over the febrile period, so that the subsequent enrichment of the blood by opsonic antibodies takes place exclusively in the afebrile period ; this certainly does not speak for an immunizing value of fever. Wright has also stated the fact, of special interest in this connection, that in the active immunization of man against enteric fever, the result does not in any way depend on the febrile reactions which so often, but not necessarily always, accompany this immunization. Experiments were also made by Naunyn, who was unable to find anatomical damage in the organs of overheated animals. His views, however, were not borne out by the work of Litten, whose results he disputed. Werkowsky and Ziegler,¹⁸ too, employing a faultless technique, discovered severe degenerative changes in the organs of overheated animals.

An explanation of these contradictory estimates of the value or danger of fever is not far to seek. I do not consider that the fever is really the sign of a primary reaction in the seat of disease but is a result of circulatory changes ; these are at the root of the fever, the blood-stream being diverted from the skin (which then gives up too

**The Value
of Fever ;
Contradictory
Estimates.**

**Circulatory
Changes
accompanying
Fever the
Helpful Factor.**

little heat) to the organs damaged by the toxin. Details of this fever theory are given in my "Lehrbuch der klinischen Untersuchungsmethoden," 6th edition, published in 1911-12. If this idea is accepted and the rise of temperature regarded as a more or less unessential sign of these circulatory events, it is not difficult to realize that the fever may sometimes have a favourable action, sometimes an unfavourable one; even in the same case and at the same time it may be both useful and in other respects harmful. The factor which is always of value in these processes is not the increased body temperature but the changed circulation which brings a richer blood-supply to the internal organs damaged by the cause of the fever and thus helps to restore them to a normal condition; it is to this factor that the organism has undergone phylogenetic adaptation. This advantageous adjustment of circulation may, however, be more than counterbalanced by the damage caused by the rise of temperature.

The conclusions we have arrived at with regard to this alleged value of fever make it quite evident that one is not justified in provoking febrile reactions in tuberculin treatment. Any possible value they may possess is certainly not present in every case; even if it were, before the real utility of febrile reactions could be proved, it would have to be shown that any power the fever might have in eliminating the damage caused by the tuberculin (just as the useful side of the inflammatory focal reactions) is not more than counterbalanced by the damage itself, and a negative balance left for the body.

It follows, then, that the tuberculin dosage should be so regulated that as far as possible both focal and general reactions are avoided. This regulation will

**Febrile
Reactions not
Justifiable.**

generally not prove a difficult matter if the rules given in this book for dosage be adhered to; experience shows that if, in spite of every precaution, slight signs of reaction result, they will be so small that no harm is done. Although the question is fully discussed in the description of the technique of tuberculin treatment, it may here be emphasized that, in addition to febrile phenomena and focal reactions, all other manifest toxic actions must be avoided by careful dosage; for these, too, are the sign that the organism has reached the limit of its capacity for resistance.

In the spontaneous cure of tuberculosis, although exactly the same forces come into play as in tuberculin treatment, it is seen that it is by no means necessary that acute inflammatory or febrile phenomena be produced; on the contrary, early tuberculosis heals more quickly in the absence of inflammatory phenomena and fever. This fact beass out the argument for a reactionless tuberculin treatment. Nägeli¹⁹ and Burckhardt²⁰ have proved the presence of small tubercular foci in the lungs and glands of nearly every adult body; foci clinically, and to some extent also anatomically, healed, and thus of no morbid significance; many of these cases have never displayed any marked inflammatory or febrile phenomena, but the disease has nevertheless been cured. This shows clearly enough that the processes of reaction which bring about a cure need not reach a point at which they are clinically perceptible. The ideal of a correct tuberculin treatment, which should simply try to copy these natural healing processes, is, then, a reactionless treatment. It is just the many disasters and failures that attend a tuberculin treatment associated with clinical reactions that have done so much to bring tuberculin into discredit.

**Proofs from the
Spontaneous
Cure of
Tuberculosis.**

We have suggested as a guiding principle that to avoid danger in tuberculin treatment, focal and general reactions, especially if accompanied by fever,

Value of a Mild Tuberculin Treatment.

must be avoided: this of course only refers to the more apparent reactions, and does not suggest the avoidance of those finer reactive changes clinically imperceptible which bring about healing in a progressive tuberculin treatment in the way we have shown. I have no doubt whatever that even in a tuberculin treatment which avoids all perceptible signs of general or local reaction, every injection after the active dose is reached produces slight hyperæmia, a slight increase of exudation, &c. Thus a mild tuberculin treatment offers all the advantages of a reactive treatment without the drawback of its danger.

Objections are sometimes raised to my view of the danger of perceptible reactions on the ground that ex-

Dangers of Forced Treatment; Kill or Cure.

perience has frequently shown that a tuberculin technique which intentionally produces clear and distinct signs of fever and inflammation often brings about a quicker cure than the mild treatment I have recommended; this is undoubtedly true, but objection must be made to the conclusions which are drawn therefrom with regard to the choice of a method of tuberculin treatment. Such a forced treatment may—if the patient is not killed by it—act more quickly than the mild treatment proposed; but it need not be assumed that this is because it is a new therapeutic agent that has been introduced in the shape of perceptible reactions; a satisfactory explanation of the fact is that when such a treatment is tolerated by the patient, the necessary degree of tuberculin action is more quickly attained. For this reason alone, a forced treatment, when it does not do harm, acts quicker than a mild

treatment, often enough not on account of, but in spite of the reactions. Further explanation is unnecessary. The recommendation of a tuberculin treatment with manifest reactions is, then, illogical; it trades on the successful cases alone, and ignores the many failures which show the reverse of the medal, and bring discredit upon tuberculin treatment in the lay mind. For the high degree of tuberculin action, especially of tox-immunity, obtained by forced treatment, can just as well be reached without manifest reactions, admittedly more slowly, but avoiding all danger. The reactive changes which bring about a cure are, as we have seen, by no means excluded by this method. In face of the dangers of manifest reactions, the longer period of treatment in a disease which is itself of long duration does not come into consideration.

Proofs of the doubled-edged nature of manifest tuberculin reactions are not hard to find: the incorrect technique responsible for the unfortunate experiences of the 'nineties almost entirely discredited tuberculin treatment for many years. Wolff-Eisner (*loc. cit.* p. 209) has collected and published a large number of cases of harmful effects resulting from the diagnostic tuberculin reaction; he rightly insists, therefore, that bad results of forced tuberculin treatment are much more frequent; further, that the ill-effects resulting both from diagnosis and treatment are only published in the small minority of cases, since the opponents of tuberculin, not using it, have nothing to report, while, on the other hand, adherents of the treatment do not publish the majority of the ill-effects produced because, under subconscious influence, they ascribe any relapse to an intercurrent aggravation of the disease independent of the tuberculin.

**Proofs of its
Double-edged
Nature.**

Reactionless tuberculin treatment, besides being free from danger, is free from unpleasantness for the patient.

A Mild Treatment free from unpleasantness.

In fact, the treatment I am recommending does not in any way diminish the working capacity of patients otherwise capable of following their usual employment. This advantage further helps to counterbalance the longer duration of treatment. Another advantage of this freedom from unpleasantness is that the really early cases, in which the prospects of success are greatest, will willingly submit only to a mild tuberculin treatment: such cases naturally do not submit to a treatment which they fear might incapacitate them, because they see the possibility of natural cure without treatment, however uncertain it may be in any particular case. I believe that there is a great future for a mild tuberculin treatment of this kind in the possibility of a kind of prophylactic treatment of the very early cases and I consider that it is destined to play just as valuable a part as vaccination in the fight against smallpox.

We have hitherto merely considered the direct action of tuberculin treatment on the foci, consisting partly of tox-immunity, partly of the stimulation of the natural healing processes of local origin.

Action of Tox-immunity on the General Condition.

We must now notice the action of tox-immunity on the general condition of the patient, an action which exerts a very indirect influence on the local morbid conditions. One need only mention the frequent poorness of appetite and the resulting decrease of general nutrition, the bad circulation, fever and other toxic actions of the disease. It is clear that if tox-immunity succeeds in getting rid of these toxic actions, the way is indirectly cleared for the cure of the disease by the natural healing processes.

Experience has shown that by means of all these factors of tuberculin treatment, successful cures can be obtained in cases not too far gone, cures which could not be made by other means or only much more slowly. If this positive experience does not suffice, an indirect proof of the special therapeutic activity of tox-immunity is found in forced tuberculin treatment which has not yet quite disappeared: the large doses of tuberculin and the resulting surcharge of toxin often enough produce a striking deterioration of the general condition and a lasting aggravation of the local condition.

I have suggested the idea of an immunizing healing action to describe the working of tuberculin. The views set forth by Landmann²¹ have compelled me to point out the difference between immunizing healing action and the immunization of a serum-giving animal. Arguing from the analogy of the latter immunization, those who merely superficially consider the question maintain that the highest possible dose of tuberculin should be reached in every case. It will be shown in the Theoretical Part (p. 185) that there is even a certain antithesis between immunizing healing action and true immunization in tuberculosis. It is very possible that the idea of an immunizing healing action, being a new one, will not always be fully understood; I must point out that it is not of my own invention, but so to speak copied from nature. Immunizing healing actions in the present sense always come into play in the natural cure of infections when such a disease as pneumonia or erysipelas is healed by reactive processes of an immunizing nature. The crises bear witness to the fact that these reactive cures are connected with immunizing processes in the form of sudden detoxication. In spite of these immunizing actions,

immunity is by no means established to these two diseases ;

**Reason for the
Non-establish-
ment of Real
Immunity.**

on the contrary, a kind of hypersensitive-
ness results which is shown by the frequent
recurrence of pneumonia or erysipelas. The
fact seems at first sight paradoxical that a
reactive immunizing cure of an infection can take place
without the establishment of true immunity. The simplest
explanation is the assumption that the reactive pheno-
mena and the resulting production of antibodies are
enough to render innocuous the cause of the disease,
whether by bacteriolytic or antitoxic action ; a healing
action is thus produced by preparing the way for the
non-specific factors such as inflammation, exudation and
accumulation of leucocytes, lymphocytes and blood-plate-
lets ; no permanent increase of antibodies must result,
however, nor is the organism rendered capable of resist-
ing future infections by an immediate mobilization of
antibodies without showing symptoms. In the case of

**An Acquired
Capacity for
more Rapid
Reaction.**

pneumonia or erysipelas, the organism un-
doubtedly does possess a special weapon
after a first recovery from the disease just
as in the case of tuberculosis ;* this seems,
however, to be merely an acquired capacity for more
rapid reaction, a hypersensitiveness which is at the
same time the cause of the relapse. The conditions in
this case are therefore diametrically opposed to those
in an immunization as generally understood, where the
organism is able to repel the virus completely. The
term "immunity by hypersensitiveness" might be intro-
duced to describe this condition or, so as not to tam-
per with the old conception of (absolute) immunity,
"capacity for resistance by hypersensitiveness." As
we shall see in the Theoretical Part, a parallel of these

* Cf. pp. 148 and 154.

events in pneumonia, erysipelas, &c., is found both in the natural course of tuberculosis and when the course of the disease is favourably modified by tuberculin treatment. In the cure of tuberculosis, in spite of the temporary immunizing processes, it is no

Proofs that no Real Immunity is produced. more a question of a real immunization in the historical sense of the word than in pneumonia or erysipelas. Three proofs of this might be given :—

(1) The frequent recurrence of the disease and the persistence of tuberculin sensitiveness after the tuberculosis has once been cured.

(2) The impossibility of immunization against living tubercle-bacilli by chemical toxins.

(3) It is shown on p. 151 that even the so-called immunity to tuberculosis obtained with living tubercle-bacilli by von Behring is not a real immunity but merely an increased power of resistance due to hypersensitiveness.

Unless this difference between immunization and the temporary immunizing processes which bring about a cure be fully understood, the treatment lacks a rational basis, and in the effort to push the tuberculin dose in every case as far as possible, harm will be done by overloading with toxin. What I have called an immunizing healing action may perhaps be better understood as a stimulation or excitation of the natural healing processes by mobilization of the lytic and antitoxic antibodies ; the simplifying term tox-immunity used before may, I confess, give rise to misunderstanding by confusion between immunization and immunizing healing action, since it covers only one factor in the complicated action of tuberculin.

The law is well known that for the production by artificial means of powerful immunizing actions, sudden

step-like actions of the antigen must take place, since it is a question of stimuli which have to pass a certain limit ;

Treatment necessitates Sudden Actions of Antigen. this law is by no means violated by a mild treatment, even though all perceptible reactions are avoided. The fact that in injection treatment the tuberculin all at once

reaches the circulation is one of the advantages of tuberculin treatment over the spontaneous absorption of tuberculin : sudden reactive actions necessarily accompany injection treatment even though they are not clinically perceptible. The mental perception alone can recognize them, but with no less certainty. It is generally accepted that in the cure of other infectious diseases such imperceptible processes of reaction play a decisive

Examples in Infections part. Who has ever actually seen the immunizing reactions in enteric fever which undoubtedly effect the cure of this infection ?

By hæmatology alone can they be recognized in the characteristic leucocyte-curve first observed by Nägeli.²³ The alternate critical days in pneumonia pointed out by Traube undoubtedly represent immunizing reactions repeated at forty-eight-hourly intervals. Yet these reactions are usually unnoticeable, and only in exceptional cases is the last decisive reaction apparent as a *perturbatio critica*, a temporary aggravation of the condition. Many examples may also be found in experimental

and in Experimental Pathology. pathology of the fact that a rich production of antibodies may take place without any manifest signs of reaction. Thus Knorr²³

discovered that the injection into the hen, a creature very insensitive to tetanus, of the tenth part of the amount of tetanus-toxin necessary to produce symptoms, calls forth a vigorous production of antibodies. I am therefore convinced that even the mildest injection

tion treatment by tuberculin, especially if the limit of tolerance is reached by a gradually increased dose, calls forth these latent processes of reaction; and, in order to prevent misunderstanding, I will again state that our knowledge of immunity and healing processes shows that reactions in this general sense are necessary for cure. On the other hand, rough experiments with manifest reactions are quite another matter and must be entirely avoided. These manifest reactions are the expression of extensive damage to the organism. I grant that they may, indeed, have favourable results, but not that they necessarily do. Even in pneumonia, a patient may be killed by the *perturbatio critica* which in other cases brings about a cure.

It will be seen that the result of tuberculin treatment in a particular case will essentially depend on whether or no the weapons afforded by the treatment render sufficient aid to the organism in its local fight against the tuberculosis and whether the natural healing factors belonging to the constitution of the patient, increased by the tuberculin, are able to destroy the tubercle-bacilli. This will depend on the state of the disease when treatment is commenced and the capacity of the organism to reply to the tuberculin by useful anti-actions; it depends, too, on whether the organism is not already sufficiently under the influence of tuberculin by the disease itself, on the general vitality and on the functional capacity of the vital organs especially of digestion, respiration and circulation. If these functions are weak from birth or subsequently undermined by the disease, the tuberculin treatment will naturally do no good. In other words, tuberculin treatment can only afford a functional assistance to the organism; only in favourable cases in which these

Prognosis in
Tuberculin
Treatment.
The Factors.

protective functions are more or less spontaneous, can it stimulate them to an actual natural cure.

One must always remember that too high a dose will incite toxic actions and cause both local and general injury, since the anti-actions of the organism are not correspondingly increased, the result being an aggravation of the disease and endangerment of the life of the patient.

This theoretical view of the nature of tuberculin treatment is the best talisman against a dangerous surcharge of toxin to which the patient may so easily be exposed if one strives to reach the unattainable goal of a true immunity to tuberculosis.

TECHNIQUE.

We have seen that it is an immunizing healing action, not a true immunization, which takes place in tuberculin treatment; by no means, therefore, must

The Optimum Dose. the dose be raised as high as possible in every case, but the optimum therapeutic dose must be determined for each patient.

This optimum dose may be defined as the maximum amount of tuberculin which can be tolerated at any particular moment without producing any ill-effects.* It will be readily understood that this is not the same in all cases, but is an individual dose for every separate case, since the treatment does not depend on the direct action of tuberculin, but rather on the anti-actions produced by the organism itself, the capacity for which is very variable. It is impossible to over-emphasize the fact that the tuberculin cure is throughout a natural healing, to which there are certain limits; these limits depend not only on the state of the disease but also on the inherited capacity

* Exceptions will be mentioned later. (*Cf.* p. 66.)

of the organism; therefore they can never be exceeded. It is, of course, evident that this maximum dose, the optimum, can be more or less raised during a tuberculin cure if the result of the treatment is successful.

The difference in principle between tuberculin treatment and the old therapeutic measures in tuberculosis (e.g., hygienic-dietetic measures, use of morphia, antipyretics, digitalis, &c.) is not so great as enthusiastic champions of tuberculin treatment seem to think. Tuberculin is not a direct cure for tuberculosis, but only exerts an influence on an underlying function, as is the case with the older measures employed. Nothing will better guarantee a correct use of tuberculin than the keeping in mind that the effect that each injection is intended to produce must be as carefully considered as in the case of digitalis. A correct tuberculin treatment demands, then, just as much observation of the patient as does digitalis treatment.

The fact is well known to every tuberculin therapist that the tuberculin sensitiveness in various patients, and even at different times in one and the same case, may vary enormously; this shows how exactly must the dosage be adapted to the individual case and how little it can be based on any general rule.

Consequently, and this brings me at once to the real technique of tuberculin treatment, the estimation of the dose and the strength of the solutions by the absolute quantity of the original tuberculin in question has absolutely no practical value. Indeed, one might point out the disadvantages of an absolute dosage as frequently used. It helps, only too easily, to support the idea that the action

**Necessity for
Careful Super-
vision of
Patient,**

**and Adapta-
tion of Dose.**

**Disadvantages
of Dosage by
Absolute Quan-
tity of Tuber-
culin.**

of a fixed absolute dose of tuberculin can be judged in just the same way as, for instance, a particular dose of morphia. I could quote many cases in which this pseudo-exactitude in the size of the dose has led to the most serious results in the hands of an inexperienced practitioner. An absolute dosage further gives occasion for quite unfair comparisons between the activity of various tuberculins; such a comparison by absolute weight is logically impossible since they consist of impure mixtures and are therefore non-comparable.

On the other hand, the problem of absolute dosage is entirely eliminated if the practitioner is provided with the tuberculin in a numbered series of dilutions of progressive strengths whose relations he knows. The doctor must then know the initial dose with the number of the solution which will always prove innocuous: an estimate of this dose will be given; if he then learns the relative strengths of the various dilutions, he will always be able to carry out a tuberculin cure correctly, guided by the results of the tuberculin action and unperplexed by any misleading problems of the absolute tuberculin content, whatever tuberculin he may be using. A knowledge of the absolute content is only necessary in the preparation of the dilutions, but for treatment it is unnecessary and even confusing.

Another advantage in a series of dilutions simply numbered according to concentration is seen in the fact that in raising the dose one obtains a gradual and regular increase not only of the absolute quantity of tuberculin but also of the concentration of the dilutions. This is of importance since the concentration of the solution injected probably plays a part in the tuberculin action,

**A Better
Method of
Dosage.**

**Method avoids
the Difficulty
of Variable
Concentration.**

just as in the case of such substances as alcohol and morphia, the chemical composition of which is known. A concentrated solution has a more powerful action than a diluted one because of the more rapid absorption, even though the absolute quantity of the active principle be the same. If the dosage is based on the absolute quantity of tuberculin, there is consequently a temptation to inject just the volume of solution which suits one's own convenience, using any dilution that may be at hand; thus at one time a particular quantity of tuberculin may be injected in low concentration, at another in high concentration; the latter injection may quite unexpectedly produce unfavourable results. This danger disappears in the employment of a continuous series of dilutions, when the volume of fluid injected and the concentration are both raised by a fixed rule.

The next question is: Should the doctor himself prepare the dilutions, or is it better for him to get them

**Should the
Practitioner
make his own
Dilutions?**

direct from the manufacturer of the tuberculin in question? The latter course seems to me far preferable. The accurate preparation of the weaker solutions is by no means an easy task for the practitioner, considering the enormously high dilutions necessary. Disastrous mistakes may so easily be made and the necessity for absolute asepsis makes it still more difficult. If the doctor does not fully understand the significance of the concentration, there is a danger that he may prepare his dilutions merely for the purpose of conveniently injecting a certain absolute amount of tuberculin, according to the measures and pipettes at hand; this will, as we have said, cause the most unexpected results due to big variations in concentration.

These questions of pure technique may seem petty to

the uninitiated but they are of fundamental importance for a correct tuberculin treatment. Without wishing to detract in the slightest from the great work of Koch, I consider that the absolute dosage of tuberculin he introduced has done a great deal to check the progress of tuberculin treatment. Denys' tuberculin is supplied to the practitioner ready for use in dilutions bearing fixed proportional rates of concentration and I believe that this fact is one of the chief reasons for the successful results obtained by this preparation, especially in Switzerland. However, the scale of dilution used by Denys has a drawback which is remedied by Beraneck in his new scale, adopted at my suggestion ; this drawback of Denys' scale will be shown.

Denys' tuberculin is supplied in eight solutions called—
Denys' Scale.
Its Drawback.

$$\frac{T_0}{10,000} \quad \frac{T_0}{1,000} \quad \frac{T_0}{100} \quad \frac{T_0}{10} \quad T_0 \quad T_I \quad T_{II} \quad T_{III}$$

In this series, each solution is ten times as strong as the preceding one. Now in consequence of this great difference between the concentrations of the various solutions, it is impossible, in passing from one to the next in order, to avoid jumps in the dose which may sometimes prove a source of danger. Let us consider this point: We will presume that the practitioner is using an ordinary 1 c.c. syringe, graduated into tenths. We will suppose he is employing one of the weaker solutions and has gradually risen, division by division,* to a whole syringe; he then proceeds to the next solution of which, according to Denys' scale, one division of the syringe is equivalent to the whole syringe of

* Division = $\frac{1}{10}$ of a syringe, that is $\frac{1}{10}$ c.c.

the previous solution. If now he proceeds as before injecting two divisions of this new solution, it is clear that the dose will be doubled. One cannot wonder that sudden sharp reactions often take place. This danger is repeated every time one passes from one solution to the next in order. Even if the danger of this big jump from the first to the second division be recognized and the amount raised by merely a quarter of a division, the dose is even then made a quarter as large again; experience has shown that this rise is often too great. In addition to this disadvantage of the scale, there is also the large increase in concentration of each fresh solution.

In order to avoid these drawbacks, I have induced Professor Beraneck to adopt the number 2 as the dilution factor for his tuberculin, that is to make each solution twice as strong as the preceding one; the concentration thus rises in powers of 2 instead of in powers of 10 as in Denys' scale, where sudden jumps were unavoidable. It is true that a much larger number of solutions is required to reach the highest concentrations, but this disadvantage is more than counterbalanced by the much finer regulation of dose possible, as I will show. Beraneck's tuberculin is usually supplied for use in 15 dilutions * which are called

**The Advan-
tages of
Beraneck's
Scale.**

$\frac{A}{128}$	$\frac{A}{64}$	$\frac{A}{32}$	$\frac{A}{16}$	$\frac{A}{8}$	$\frac{A}{4}$	$\frac{A}{2}$	A	B	C	D	E	F	G	H
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Each solution is, then, twice as strong as the preceding one. The use of fractions arises from the fact that experience proved the necessity for weaker and weaker solutions; fractions were used to avoid changing the

* The employment of still weaker solutions will be considered later.

original designation of the solutions. The strongest solution for treatment (H) is 62·5 times weaker than the original concentrated tuberculin Beraneck; as is the custom with other tuberculins, I have called this "tuberculin," or, to avoid mistakes, T.Bk. (Tuberculin Beraneck). The scale of solutions beginning with the strongest then runs as follows :—

**Absolute
Tuberculin
Content of
Solutions.**

H = T.Bk. (Tuberculin Beraneck).		
G = $\frac{\text{T.Bk.}}{2}$	$\frac{\text{A}}{2} = \frac{\text{T.Bk.}}{256}$	
F = $\frac{\text{T.Bk.}}{4}$	$\frac{\text{A}}{4} = \frac{\text{T.Bk.}}{512}$	
E = $\frac{\text{T.Bk.}}{8}$	$\frac{\text{A}}{8} = \frac{\text{T.Bk.}}{1024}$	
D = $\frac{\text{T.Bk.}}{16}$	$\frac{\text{A}}{16} = \frac{\text{T.Bk.}}{2048}$	
C = $\frac{\text{T.Bk.}}{32}$	$\frac{\text{A}}{32} = \frac{\text{T.Bk.}}{4096}$	
B = $\frac{\text{T.Bk.}}{64}$	$\frac{\text{A}}{64} = \frac{\text{T.Bk.}}{8192}$	
A = $\frac{\text{T.Bk.}}{128}$	$\frac{\text{A}}{128} = \frac{\text{T.Bk.}}{16384}$	&c.

I hope that this statement of the absolute tuberculin content of the various solutions will satisfy those of my colleagues who have applied to Professor Beraneck for information on this point. As in the first edition of this book, however, I again state that questions of the absolute tuberculin content of the solutions are of no importance for the practitioner and only lead to confusion; for what we call the original tuberculin solution or pure tuberculin is merely an arbitrary concentration of an actual pure tuberculin still unknown, and its strength depends entirely on the method of preparation. In the first instance, Beraneck published the actual tuberculin content in parts by weight of a fluid called $\frac{\text{T}}{20}$. This was a solution of convenient strength for the preparation of dilutions and was so called because it was a 20 times dilution of concentrated tuberculin Beraneck. Solution H or the present pure tuberculin Beraneck corresponds to a 3·125 times dilution of $\frac{\text{T}}{20}$ and is thus 62·5 times weaker than the so-called concentrated tuberculin Beraneck.

Still weaker solutions than those mentioned are sometimes required for the treatment of specially sensitive patients, and these are always obtainable without trouble

from the place of manufacture. The advantages of this scale of dilution are apparent. The dosage can be regulated five times more finely than in Denys' decimal scale. In passing from one solution to the next, half a syringe of the stronger solution is equivalent to a whole syringe of the weaker. The dose can from this point* be increased by $\frac{1}{20}$ by going up by $\frac{1}{4}$ of a division, which can be easily estimated with a suitable syringe. Experience shows that this increase by $\frac{1}{20}$ is never excessive; the increase of dose becomes even less as one advances by $\frac{1}{4}$ divisions to the end of the syringe. Figs. 1 and 2 illustrate the difference between Denys' scale and that now adopted by Beraneck. They show the possibilities of graduation on both scales, it being supposed that the dose can be increased quite regularly throughout the treatment, an ideal which is unfortunately never attained in practice. To make the matter clear, in passing from one solution to the next, I have inserted the dose of the latter equivalent to the whole syringe of the former; this is, in the first case (Denys' scale), $\frac{1}{10}$ of a syringe and in the second (Beraneck's scale), $\frac{1}{2}$ of a syringe, from which point the dosage proceeds as before. These equivalent doses are represented by the horizontal "steps" in the figures. To avoid misunderstanding, I must point out that fig. 2 does not represent the actual scale of dosage I recommend but is merely to show the possibility of a very fine graduation of dose. Lack of space has compelled me to represent the dose as rising by a whole division,

* In actual practice, one does not begin with half a syringe, but with a much smaller amount, as will be shown later. I only want to show the possibility of a very fine graduation of dose.

but in practice it rises merely by $\frac{1}{2}$ or $\frac{1}{4}$ of a division, which would make the curve considerably longer and represents a still finer graduation. The diagram shows, however, the possibility of a gradual and quite regular rise of dose and a comparison with fig. 1 shows its superiority in this respect to Denys' scale. The actual course of dosage will be shown in fig. 3.

Diagrams to show the possibility of graduating the dose on Denys' and Beraneck's scales of dilution; the weaker solutions only are illustrated.

The respective rises of dose at *a* and *b*, after passing to a fresh solution, should be noticed; in fig. 1 (Denys') the dose is doubled while in 2 (Beraneck's) it is only raised by $\frac{1}{2}$. The diagrams could not be extended further than the commencement of the third solution since curve 1 here becomes nearly asymptotic. Misunderstandings having arisen, I will repeat that fig. 2 does not represent the actual course of dosage which will be shown in fig. 3.

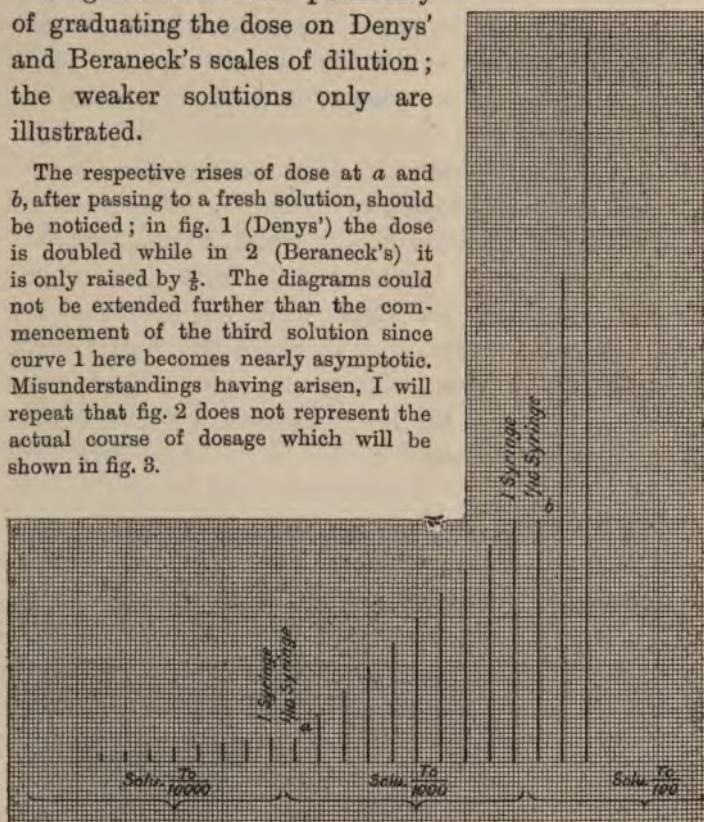


FIG. 1.—GRADUATION OF DOSE ON DENYS' SCALE.—This shows the very rapid rise of dose and the danger of overloading with tuberculin even when the greatest care is taken.

The advantages of a scale rising by powers of 2 are so great that I should like to see it adopted for other tuberculins, especially Denys' and Koch's. These dilutions, then, in which Beraneck's tuberculin is supplied to the practitioner, very much simplify the technique, exclude all possible mistakes and do away with undesirable jumps in the dosage; these advantages alone, apart from others still to be considered, have led me to give the preference to Beraneck's tuberculin.

The dose of such a tuberculin as Beraneck's, containing the bacillary protein as a true solution of an acid albumin,

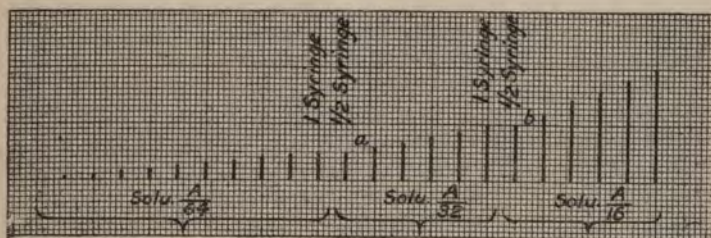


FIG. 2.—GRADUATION OF DOSE ON BERANECK'S SCALE.—A much more gradual and regular rise, materially decreasing the danger.

The vertical lines denote the absolute doses of tuberculin. One syringe = 1 c.c. A whole division of the syringe ($\frac{1}{10}$ c.c.) is taken as the rise of dose on account of lack of space. If a rise of dose of merely $\frac{1}{4}$ division ($\frac{1}{40}$ c.c.), the finest graduation possible, were taken as standard, the curves would extend further in length; the difference in principle, however, between the two curves would be unaltered.

can be much more finely regulated than that of a bacillary emulsion, as in the preparation of high dilutions of the latter one can never be sure of the regular graduation of the solutions in view of the possible inequality of mixture. The other properties peculiar to this tuberculin are mentioned in the Theoretical Part (pp. 117-123); on account of these and the advantages already mentioned, I prefer to

PRACTICAL PART

use Beraneck's tuberculin in treatment to all other tuberculins, although I acknowledge the active principle of every tuberculin is the same.*

In connection with this discussion of the importance of a finely graduated dosage, I should like to point out how inappropriate is the dispensing of tuberculins in ampullæ ready for injection, a practice which has lately come into vogue. It is clearly impossible to obtain a fine graduation of dose by such a method, and the practitioner will seldom secure for himself a finer graduation by dividing up the content of an ampulla, since this would destroy the only possible advantage of such a method. The form of dispensation is evidently intended to indicate a single dose. This method of supplying tuberculin does not fit in with a rational method of treatment, and I do not doubt that the errors of dosage necessarily connected with it will help to discredit tuberculin treatment. I am told that in Russia the dispensing of tuberculin is only permitted in the form of ampullæ! The intention of this law may be good, but it nevertheless defeats its own end, and is a source of danger. It is possible that there is some hazy idea that estimates of absolute dose are necessary as in the case of sera. Tuberculin is, however, not a serum nor does it resemble one in its method of employment. An estimation of the amount of tuberculin for a patient and its supply in ampullæ is naturally unworkable and, indeed, absolutely impossible, since the action of a certain dose of tuberculin will depend entirely on the individual sensitiveness of the patient, which must first be ascertained. There is clearly no purpose in putting up a remedy, whose dosage is so entirely individual, in measured vessels like the ordinary necessities of life. Practitioners who are not well up in the question of dosage feel a kind of security in this pseudo-exactitude, which is, however, both fallacious and disastrous.

One other point in the technique must be observed. Many tuberculins including Beraneck's contain no anti-septic, so that aseptic precautions must be taken in the injections. This can easily be done by keeping the syringe

* An exact clinical comparison of the therapeutic value of the various tuberculins will only be possible when a uniform method is accepted as the basis of the comparative tests. Not only should reactions be avoided but also the 2-scale of dilution be adopted. As long as no uniform method is adopted, one is comparing things which are non-comparable, arguing about the Kaiser's beard.

with its glass or metal piston* in absolute alcohol after once boiling it thoroughly. It is necessary to wash out all traces of alcohol with sterile water, since even small quantities of alcohol precipitate the tuberculin solutions. The safest method of all would be to boil the syringe each time; the solutions could not then possibly be rendered unsterile by contact with the needle; time and circumstance, however, may not permit of this refinement. To ensure accuracy of dose, the syringe and needle should be washed out each time after use with sterile water; traces of a stronger solution cannot then increase a subsequent dose of a weaker solution. This must be done, even if the syringe be boiled every time, as tuberculin is, at any rate to a certain extent, stable on heating. If the syringe is fitted with a metal piston, this washing out should be done immediately after use, since Beraneck's solutions, especially the stronger ones, have a slightly acid reaction and may attack the metal if left long in contact with it. To keep the solutions aseptic, in withdrawing the fluid from the bottle, the needle only should be dipped in. The bottles should not remain open longer than necessary; the cork should not be touched except on the top, and in opening the bottles care must be taken not to let little pieces of the wax used to seal them drop into the fluid. Solutions which, in course of use, have become cloudy by bacterial growth, naturally must not be used but should be replaced. However, if the foregoing precautions be observed, one has no

* A tuberculin syringe of the pattern I recommend is supplied by the firm of Schärer, A. G., Sanitätsgesellschaft, Bern. In contrast with the ordinary syringe, it has a metal piston with a spring which prevents it from slipping down by the action of gravity; it is easily sterilized, holds 1 c.c. and is graduated sufficiently finely for tuberculin treatment. Each $\frac{1}{10}$ c.c. is numbered and subdivided into two; $\frac{1}{20}$ c.c. can be quite easily estimated.

difficulty in keeping Beraneck's solutions permanently aseptic. As the solutions probably do not retain their activity for an unlimited length of time, they are prepared fresh at the laboratory on receipt of order. For this reason, Beraneck's tuberculin is not supplied by agents but only direct from the laboratory at Neuchatel.* One is thus certain of getting only perfectly fresh solutions. On the same ground, Beraneck recommends that even unopened bottles be replaced after three months. The bottles should be kept in the dark.

**Stability of
Beraneck's
Tuberculin.**

The skin of the thorax is the best place for injection, as it is the least sensitive. Injections should be made in the morning, as a rise of temperature can most easily be seen in the evening. Before and after injection, the skin should be simply dabbed with a 1 in 1,000 alcoholic sublimate solution.

Site of Injection. Disinfection of Skin.

I use this method for injections of all kinds in preference to the ordinary method of rubbing the skin thoroughly with an antiseptic, as it is a matter of common knowledge that even this rubbing does not produce a real disinfection of the skin and in any case the question of a real disinfection does not arise for a mere skin puncture. The aim in such injections is rather only to introduce into the puncture a trace of antiseptic (or of some substance hindering bacterial growth) to prevent the penetration of micro-organisms from the outside. Therefore the injection is made through a layer of sublimate solution and after removing the needle a little more is dabbed on the puncture without rubbing. An alcoholic solution is more suitable for this purpose than a watery solution, as it adheres more readily to the skin.

The injections must be subcutaneous, not intracutaneous. It is not necessary to apply plaster to the wound.

As we have seen, the plan of treatment is to begin the cure with the smallest dose of one of the weakest

* Beraneck's tuberculin is now obtainable in this country. (*Cf.* Translator's Preface.)

solutions (*cf.* p. 48) which will always prove harmless, and then the dose is raised quite gradually.

Method of
Dosage. Absolute and Individual Maximum.

The question of the length of time between each dose will be considered later. The raising of dose must be done in such a way that no manifest toxic actions (so-called reactions) ever occur, or, if they are not to be avoided entirely, they must be reduced to a minimum. These reactions will be described in detail in a later section. As soon as any such phenomena occur, be they ever so insignificant, the next dose of tuberculin must be reduced, the interval between the doses increased and the treatment subsequently carried on with greater precaution.

The dose is gradually raised till one reaches either:—

(1) The absolute maximum dose *i.e.*, a syringeful of the strongest solution; or, if the sensitiveness of the patient will not permit of this,

(2) The individual maximum dose. This must be found for each separate case according to the state of the disease. It will be one that can be tolerated without any ill-effects, but cannot be exceeded without producing unfavourable results. When this individual maximum dose has been once reached, it is repeated at certain intervals, but not exceeded. Exceptions to this rule will be mentioned under optimum dose, p. 66.

Experience shows that by a tuberculin treatment carried out on this general plan, the conditions for natural healing with which we are concerned are often considerably improved. The question of how long one should prolong the injection of the highest doses will be discussed later.

Inside this ground-plan of treatment there are several details to be considered. In the question of dosage, I shall refer only to Beraneck's tuberculin (*cf.* fig. 3, p. 50).

A routine initial dose for non-febrile adults is $\frac{1}{20}$ c.c. of Beraneck's solution $\frac{A}{64}$.* For delicate patients and non-febrile children with hereditary weakness or scrofula, for whom a prophylactic treatment may do so much, it is better to begin with a still weaker solution; for instance, in children over 6 with $\frac{A}{328}$, or under 6 with

$\frac{A}{512}$, the dose being raised in the ordinary way. With febrile adults, I always begin
Initial Dose. with $\frac{A}{328}$, with febrile children, $\frac{A}{512}$ or $\frac{A}{1024}$. It is shown in the Theoretical Part,

p. 147, that by the quantitative employment of von Pirquet's cutaneous reaction the sensitiveness to tuberculin may be gauged and an estimate made of the initial dose. This initial dose should be repeated two or three times at intervals (*cf.* below) to show that no summation reaction is produced. If signs of reaction appear, one must wait until they have disappeared and reduce the dose to $\frac{1}{40}$ c.c. of the same solution ($\frac{A}{64}$) or even employ

a weaker one ($\frac{A}{128}$ or $\frac{A}{256}$). If no reaction
Increase of Dose takes place, each following injection is increased by $\frac{1}{20}$ c.c. until one reaches $\frac{1}{2}$ c.c. of $\frac{A}{64}$, which dose is repeated several times.

If, during this time, any reactions occur, these must be allowed to subside and the treatment recommenced with a smaller dose. How big this reduction should be will be considered later. If, as is not seldom the case, the patient acquires a hypersensitiveness to the tuberculin (*cf.* p. 53) and reacts even to the reduced dose, the reaction must be given time to subside, and a further

* With patients whom the cutaneous reaction (*cf.* p. 147) shows to be specially sensitive. I now begin with even weaker solutions, viz., for afebrile cases $\frac{A}{512}$, for febrile cases $\frac{A}{1024}$, as even the latter sometimes produces reactions.

reduction of dose made. If $\frac{1}{2}$ c.c. of $\frac{A}{84}$ is tolerated several times without reaction, one proceeds to the next solution $\frac{A}{82}$, double as strong. In order to eliminate the influence of the raised concentration and to give the organism some respite, the next dose is reduced and only $\frac{1}{10}$ c.c. of $\frac{A}{82}$ injected : then onwards, with the same precautions against reaction, by $\frac{1}{20}$ c.c. until $\frac{1}{2}$ c.c. of $\frac{A}{82}$ is reached. This, again, is repeated several times if it is tolerated well ; if not, it is reduced and then gradually increased again up to the same point and repeated as before. Then one passes to $\frac{A}{16}$, giving $\frac{1}{10}$ c.c. as before and rising by $\frac{1}{20}$ c.c. to $\frac{1}{2}$ c.c. of $\frac{A}{16}$, repeating this, if well borne, several times. Thus one eventually reaches

either the maximum of tolerance (the individual maximum dose) or, where possible, the absolute maximum dose, 1 c.c. of the strongest solution H, pure tuberculin Bera-neck. In another section, I shall describe an individual therapeutic optimum, and under certain circumstances it may be advisable to go back to this dose ; the point is discussed on p. 66.

Although the principle of this scheme of dosage is the same as that described in the first edition of this book,

there are some essential alterations in the details of the method. These were necessary chiefly because I found that misunderstanding arose and the treatment was not carried out with sufficient precaution. Further, I discovered that the greatest care was necessary in drawing up rules for the use of those who have not had much practical experience in tuberculin treatment ; for this reason, I have suggested the temporary decrease of dose in passing from one solution to the next in order of concentration. There was also a third more practical reason

**Method Im-
proved in the
Light of
Experience.**

for the change, which seemed imperative when I realized what a varied selection of syringes, often very imperfectly constructed, were used for tuberculin injections. In the old scheme I recommended the use of the second half only of the syringe, from 0.5—1 c.c. for every solution except the weakest; I suggested that one should proceed from the whole syringe of the weaker solution to the half syringe of the stronger, increasing this up to a whole syringe and so on. Unless the syringe acted faultlessly, this proved impracticable, as it assumed that the syringe could be completely filled to 1 c.c. This was by no means easy with all syringes, as so often the washer and

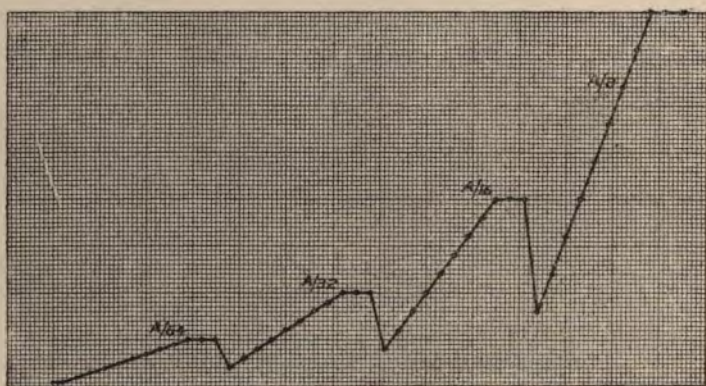


FIG. 3.—ACTUAL DOSAGE OF TUBERCULIN BERANECK, SHOWING THE REGULAR GRADUATION OF DOSE.

Horizontally, each little square = one day; vertically = the antigen-content of $\frac{1}{32}$ c.c. of $\frac{1}{64}$. Thus the actual volume of solution injected is only represented for $\frac{1}{64}$.

needle-head, especially the latter, do not fit tightly enough, and air is drawn in with the fluid; it is impossible or at any rate very difficult to get rid of this. If only $\frac{1}{10}$ c.c. of air is drawn in and cannot be removed, it is impossible to inject a whole c.c. of the tuberculin solution with a syringe which only holds just that amount. It therefore seems more practical only to use the first half of the

syringe, from 0—0·5 c.c. as described. This of course does not apply to the strongest solution H which, however, is not by any means always used. A small amount of air in the syringe will not then prevent the injection of the full dose, as at any rate half the syringe can be filled with the fluid.

Landmann²⁴ has expressed the opinion that tuberculin treatment must be carried out on more or less the same lines as the immunization of a serum-giving horse: he did not agree with my custom of reducing the dose in order to give the patient time to "recover" (*cf.* fig. 8), but probably considered this entirely unscientific; he stated that such a "recovery" is more easily attained by allowing a longer interval to elapse between the injections. I do not believe in this method, unless, of course, I am driven to it by reactions—except when giving larger doses which one assumes will last a longer time—for the following reason: the whole object of my tuberculin treatment, which is the finest example of a natural cure, is to copy the natural course of cases which heal spontaneously. Clinical experiences in such typical intercurrent infections as pneumonia, erysipelas and malaria, and the periodic temperature-curves peculiar to epidemic meningitis and the natural course of tuberculosis, all point to the fact that the negative and positive phases of immunity, toxin-actions and antibody-actions, follow each other in periodic curves in the spontaneous cure of infections. The big daily variations of temperature and the night-sweats of tuberculosis are clearly the expression of such a periodicity. I attempt, therefore, to imitate this curve of toxic action by these reductions of dose. A complete stoppage of the supply of toxin does not correspond to the natural conditions. If this reduction of dose in passing from one solution to the next succeeds also in counterbalancing the influence of the increased concentration, this is all the better.

This course of dosage is naturally only to be regarded as a rough scheme which may have to be modified to suit the individual tolerance. For instance, if the tolerance is good and no reactions occur to compel a reduction of dose, increases of $\frac{1}{10}$ c.c. may often be made instead of $\frac{1}{20}$ c.c.; this will materially shorten the duration of treatment. In sensitive patients, on the other hand, the rise of dose

**Justification
for Periodic
Decrease of
Dose.**

**Modifications
in the
Dosage.**

LANDMANN

must often be reduced to $\frac{1}{40}$ c.c. Fig. 3 shows the actual course of dosage in absolute quantities of tuberculin as contained in $\frac{A}{84}$ and illustrates the graduation I have recommended; the supposition is made that no reactions occur to prevent the ideal regular raising of dose.

With regard to the frequency of the injections, I recommend that these should be given not more often than twice a week; in the case of the stronger solutions (perhaps from C onwards), only once a week, and after the maximum dose is reached, as seldom as once a fortnight.

**Frequency of
Injections.**

We know from experiments in all kinds of immunizations that after an immunizing dose of toxin, unless quite a small one, the organism always takes a not inconsiderable time to overcome the toxic action and fortify itself against it by forming the necessary amount of antibodies. Consequently, the immediate result of an injection of

toxin is a so-called negative phase of immunity (Wright) during which the organism is in a state of hypersensitiveness, having

**The Negative
Phase.**

used up its antitoxic substances. Only when the organism is again enriched by these antitoxic substances, does the positive phase occur, which is evidenced by decreased sensitiveness. These considerations clearly show that if the injections are too frequent, there is a danger of overloading with toxin. Therefore if the tuberculin doses are of any considerable size, time must be allowed for the organism to recover from each separate dose; experience shows that this generally takes at least three days if no reaction occurs or only a very slight one; on the other hand a much longer time is necessary if there are any considerable signs of reaction.*

* By his method of estimating the opsonic action of the serum, Wright has shown the length of the negative and positive phases of

In the way mentioned, in favourable cases one can occasionally advance to the absolute maximum dose, without the patient ever exhibiting signs of reaction or evidences of any damage due to the tuberculin ; I consider a syringe-ful of solution H, pure Tuberculin Beraneck, as the absolute maximum, and I have never given more than

**Reactions—
Their
Significance**

this. In these cases, striking progress is often made in the improvement of the condition. However, things do not always go on smoothly. Sometimes more or less pronounced signs of reaction appear, occasionally even with the smallest doses ; they show that the organism is not yet able to deal with the particular dose of toxin with respect to its production of antibodies ; these reactions are described later. It is clear, then, that the following doses must be reduced to avoid any unfavourable results. It is by no means sufficient to go back to the last dose but one, which was well tolerated : because experience teaches that the consumption of antitoxin during a reaction may leave the body a negative balance for its immunizing forces ; the patient will then be hypersensitive to the next injection and harm may easily be done unless great care is taken. In many cases, this negative phase is quickly succeeded by a rise of the tox-immunity. Frequently, however, this takes place but slowly, and sometimes not at all. As this cannot be foreseen, when a reaction occurs one has to reckon with the possibility of a hypersensitiveness of long duration and it must be realized that a dose, previously well borne, may no longer be tolerated. Therefore, it seems to me that the safest

immunity in tuberculin treatment ; thus he has established the fact that after the more pronounced tuberculin reactions, the opsonic index is often found to be lowered many days after the fever has subsided, which he considers to be the sign of long duration of the negative phase of immunity.

course is to reduce the dose by at least a half after at all a pronounced reaction. In merely slight reactions, a smaller reduction may sometimes suffice. Any hard and fast rules for this cannot be given, for everything in tuberculin treatment is individual. Unless one has had a good deal of personal experience in the matter, the best rule to follow is: better too little than too much tuberculin! This cautious procedure naturally prolongs the treatment, but it has the advantage of absolute freedom from danger. Good estimates of sensitiveness and the necessary reduction of dose can be made from observation of the way in which a patient has recovered from previous reactions.

**Occasional
Necessity for
Temporary
Suspension of
Treatment.**

In very pronounced reactions it is also advisable, after the reaction has subsided, to omit one or two injections and give the patient complete rest for at least a week: under all circumstances, before a fresh injection is given, all signs of reaction must have subsided for at least two days.

Cases are sometimes met with whose sensitiveness is so great that even starting with quite a low dose and graduating it most carefully, reactions nevertheless occur again and again, and the hypersensitiveness so increases that a moderate reduction of dose is insufficient to restrain the reactions. In these cases the cure must occasionally be recommenced from the very beginning with the lowest doses. By this means, the goal of tox-immunity is often eventually reached. Cases are by no means infrequent in which the greatest difficulty is experienced in obtaining tox-immunity to the low doses, but if once a foundation is laid of tox-immunity, there is but little difficulty in the way of progress.

**Recommence-
ment of
Treatment
from beginning
occasionally
necessary.**

It must, however, be thoroughly understood that there are also cases in which no tox-immunity can be obtained, which display reactions time after time and are quite unsuited for tuberculin. These cases are by no means infrequent and nothing has more discredited tuberculin treatment than the assumption that the best path to the cure of tuberculosis is in every case that of tuberculin.

These very cases whose hypersensitiveness makes them unsuitable for tuberculin treatment, often offer all the more favourable prospects for spontaneous cure: the organism is clearly tuberculinized to the limit of its capacity for resistance, and we shall see in the Theoretical Part that a certain degree of hypersensitiveness is just the condition for the spontaneous cure of tuberculosis. One can by no means always foretell whether a case is suitable for tuberculin treatment or not; cases which are slight from a clinical point of view are often unsuitable, while sometimes a really bad case gives a strikingly favourable result.

The cases which cannot be treated by tuberculin must be distinguished from those in which good progress is made at the beginning but a certain low or moderate dose cannot be exceeded without causing reactions and running the risk of doing harm if the dose be pushed further.

These cases with a low individual maximum dose are by no means the most unfavourable for tuberculin treatment and much good is often done by the smallest doses of tuberculin; satisfactory progress is made by the frequent repetition of these low individual maximum doses at the usual intervals, the benefits of the raised tox-immunity being maintained or even increased. These cases are good illustrations of the statement that

tuberculin treatment is not an active immunization, pushed to its furthest limits, but rather that the essence of the treatment is to stimulate the natural factors and promote the cure by means of the natural functions of the body. This can often best be done by quite small quantities of tuberculin. If, during the general improvement in such cases, careful tests made from time to time show that the individual maximum dose (*i.e.*, the tox-immunity) increases, there is clearly no objection to an attempt to drive this tox-immunity still further and gain new ground; however here, as in all therapy, care must be taken not to lose the good in striving for the better, not to harm the patient by a surcharge of tuberculin and thus lose all the ground previously won. Experience teaches that there are cases which even the most careful and persistent efforts are unable to bring over a fixed individual maximum dose; they tolerate, for instance, $\frac{4}{10}$ c.c. of solution A extremely well, but react again and again to $\frac{5}{10}$ c.c. of the same solution.

**Possibility of
Subsequent
Increase of
Tox-immunity.**

It is impossible, therefore, to lay down any hard and fast rules for tuberculin dosage, as the individual sensitiveness of a patient is different at various times.

**Sensitiveness
increased by
Indisposition
of every kind.**

A proof of this is seen in the experience that this individual sensitiveness may be considerably increased during every inter-current indisposition.²⁵ * Every cold, every dental abscess, every attack of indigestion, every infection and also the approach of menstruation† may all have this effect. Especially an aggravation of the tuberculosis itself raises

* In connection with this fact, Burckhardt found that the sensitiveness to tuberculin is raised during convalescence from nearly all acute diseases. This is probably to be explained by the fact that any general weakness diminishes the capacity of the organism to form antitoxic substances.

† Cf. p. 61, note *re* premenstrual rise of temperature.

the tuberculin sensitiveness. During all such indispositions, from whatever cause they arise, the injections should be discontinued entirely and the treatment subsequently recommenced as if a tuberculin reaction had taken place; the dose must therefore be reduced or, in the case of really serious indisposition, the cure begun again with great care from the smallest doses. Unfortunately, this rule is not always observed.

It is clear from what we have seen of the dangers of the more pronounced reactions, that the recognition of even the most insignificant toxic phenomena plays a great part in a correct tuberculin cure. This seems a fitting opportunity to describe the clinical characteristics of these reaction phenomena, so that they may be easily recognized. Many tuberculin therapists simplify the matter by considering a rise of temperature the only reaction. This would make things extraordinarily easy, since the estimation of dose could be made by simply consulting the temperature chart. This conception is clearly illogical. In the first place the so-called local reactions or, better, focal reactions are overlooked and these are at least as important as the temperature. Besides, there are many other toxic actions which must be considered as signs of reaction in estimating the dose, reactions which often demand special care and a reduction of dose even in the absence of any rise of temperature or manifest focal reaction.*²⁶ Nevertheless, it must be granted that a rise

* This is confirmed by the researches of Lawson and Stewart on the influence of tuberculin on the opsonic power of the serum. They have shown that a tuberculin injection produces a fall in the opsonic index to tubercle-bacilli even when the temperature remains normal. This quite agrees with the discovery made in my clinic that leucocytosis may accompany a tuberculin injection as a sign of reaction without any rise of temperature (*cf.* p. 64).

of temperature after an injection affords the clearest proof and measure of a toxic tuberculin action and these temperature reactions must therefore be discussed.

If the temperature is to give correct information with regard to the action of the tuberculin in any given case,

it must be taken at regular intervals and at least twice a day. This should generally be done at nine o'clock in the morning and at five in the evening, commencing at least a week before tuberculin treatment is begun. It must be noted, however, that in tuberculosis the usual daily temperature curve is not always present, and it is therefore better to find out the times of maximum temperature by experiment and to take it at these hours. The maximum is not infrequently found during the morning, after the midday meal, or in the middle of the night. These conditions are probably governed by the varying influence of digestion and absorption and by expectoration. Their non-recognition or non-observance may result in fever being overlooked; this will give rise not only to errors of diagnosis in the recognition of early tuberculosis but also to mistakes in the carrying out of the treatment. I should recommend that for patients put down as afebrile on two estimations only, at nine and five, but who nevertheless exhibit a high pulse-rate, night-sweats or sleeplessness, the temperature should be taken for example after the midday meal or in the middle of the night. For reasons which I have often given, I consider axillary temperatures more reliable than mouth temperatures; it is presumed that the patient is not so thin that the armpit cannot be properly closed and that the temperature is correctly taken. I cannot discuss the correct measurement of temperature here,

The Temperature.
When it should be taken.

Axillary Preferable to Aural Measurements. Minute Thermometers!

but refer to my "Text-book of Clinical Methods": a warning against the so-called "minute measurements" must, however, be given as this phantom still seems to haunt the practitioner. There are neither minute thermometers nor minute estimations!

In cases where fever is suspected but where the usual method fails to show any rise of temperature, careful

Rectal Temperature. rectal measurements are advisable as, in many cases, fever can only be proved by this means. The temperatures must be

accurately recorded and it is advisable to keep a chart, which can be done by the patient himself. On this chart should be entered the weight and the tuberculin injections with the dose given

Keeping the Chart. (solution number and divisions of syringe, but not absolute quantity of tuberculin), and, in addition to rise of temperature, all other

signs of reaction or kindred phenomena which will be described shortly. These notes must be carefully kept and a copy should be made, possibly by the patient himself. This may be useful to the doctor for the carrying out of the treatment or at a later date to some other practitioner.

In order that even the smallest rises of temperature shall not escape observation, the injections should be

Morning Injections. When to expect Reactions. made in the morning. With afternoon or evening injections it is to be feared that the customary morning drop of temperature may obscure any rise, whereas if the tuberculin be

given in the morning any rise of temperature will usually be clearly seen the same evening. The rise may, however, take place in the night, when, if the patient feels at all unwell, the temperature should be taken. A rise after twenty-four hours or even two days is not uncommon.

An explanation of these deferred signs of reaction is given in the Theoretical Part (pp. 137 and 178). Although these late reactions call for special care in dosage, they do not necessitate such a large reduction of dose as immediate reactions.

A question which calls for most careful attention is how large a rise of temperature must be to rank as a febrile reaction. A rise of merely 4-5 tenths

Rise of Temperature as a Reaction. of a degree F. or 2-3 tenths of a degree C. must be considered as a febrile reaction if

the time of its occurrence clearly shows that it is the result of an injection, that is to say if it occurs on the day of injection or the following day: this rise is still to be considered as a reaction even when the temperature never exceeds 98.4° F. or 37° C. These comparative measurements must, of course, be taken at the same time of day. Such small rises of

Summation Reactions. temperature are often neglected and no alteration made in the dosage. It is, of course, quite true that no considerable harm

can result from such small tuberculin actions; the objection is, however, that experience shows these small reactions to be a warning sign; it often happens that if they are neglected and the dose increased as usual, the practitioner is surprised by a sudden acute summation reaction after one of the following injections, resulting from the hypersensitiveness of the patient. These may do a good deal of harm and put the patient back. It is often alleged that these febrile reactions are unexpected and therefore unavoidable; in reality, they are foretold by the insignificant reactions following the preceding injections and they can therefore be foreseen and avoided by the exercise of greater care.

We have seen that intercurrent indisposition calls for

considerable modification of the treatment. In the same way, any rise of temperature calls for special care in the treatment and a reduction of dose, even if this rise is not believed to be the result of tuberculin action: the

**Precautions
in Febrile
Reactions.**

tuberculin sensitiveness increases here just as in any other indisposition. It can easily be conceived that any lowering influence or even sometimes an aggravation of the tuberculosis itself may lessen the capacity of the body to reply to the lysinized tuberculin by the production of antitoxic antibodies. To these influences

**Premenstrual
Fever.**

belongs the rise of temperature just before the menstrual period in the tuberculin treatment of women. Its significance is very uncertain as it is quite common without tuberculin treatment, but it is best to be specially careful with any reactions at this time, even if one is not absolutely convinced that the rise is caused by the tuberculin, since it is certain that the sensitiveness is increased (*cf.* p. 56).

The term "ovulation fever" has been used to describe a spontaneous premenstrual rise of temperature. We are, however, not yet certain whether it is a physiological rise caused by the process of ovulation or whether there is present some infection especially of a tuberculous nature, which is aggravated just before each period. According to my theory of fever (*cf.* "Text-book of Clinical Methods," 6th edition, 1911-12), the phenomena are easily explained by assuming that the hyperæmia of the pelvic organs resulting from ovulation decreases the cutaneous circulation and thus lessens the amount of heat lost.

There are still other cases in which no isolated sharp reactions follow the injections but the temperature gradually rises during the treatment. This

**Significance of
a Gradual
Rise of
Temperature.**

can be ascribed to a summation reaction and is caused by the gradually increasing hypersensitiveness: the organism is not able to respond to the rising lytic actions by the production of antitoxin. Even where there is no exact

proof of this conception, it is prudent to consider such a gradual rise of temperature as a febrile reaction, as we have just seen that even intercurrent affections, especially if they depend on the tuberculosis itself, call for just as much care in treatment as definite tuberculin reactions.

In addition to the influence of tuberculin on the body temperature, there are many other phenomena to be considered if one is to be sure of recognizing

Other Signs of Reaction.

the very smallest toxic action of the tuberculin, correctly adjusting the subsequent treatment (*cf.* pp. 9-10) and reducing the dose at the right moment. Thus an appreciably raised pulse-rate or the occurrence of dyspnoea after an injection must be considered as the expression of a toxic action demanding special care or, to use the common optimistic term, a tuberculin reaction. Under this heading must be included any general indisposition shown by loss of appetite, depression or sleeplessness, and so often accompanied by headache. I consider that all these are general toxic actions of tuberculin, generally known as tuberculin reactions, and they have the same significance as fever. To ensure their recognition, it is necessary that the practitioner in charge of the case should take the trouble, before each injection, to inquire whether the patient has felt at all unwell, although no previous complaint may have been made. These indispositions must be considered as reactions even if it is not absolutely certain that they are caused by the tuberculin.

Any progressive loss of weight occurring during the treatment, even if the patient is quite afebrile, shows the necessity for reduction of dose or even

Loss of Weight.

a temporary suspension of the injections. It is frequently the sign of chronic tuberculin cachexia, a condition too little known and

often overlooked : like the reactive phenomena which are caused by irritative actions and soon subside, it shows that the body is overloaded with toxins. The patient should therefore be weighed once a week both before and during the cure.

In addition to these general phenomena, there are the organ or focal reactions of the tuberculous organs to the tuberculin ; they, too, show that the organism is in danger of being harmed by the tuberculin. An increased cough and sputum after an injection, traces of blood in the sputum or an actual hæmoptysis, pleuritic pains, swelling of tuberculous glands, increase of inflammatory redness in visible places, such as in tuberculosis of the skin ; all these are signs of a toxic tuberculin action and demand a reduction of the dose. Here again, the dose should be reduced even if one is not absolutely certain that these symptoms are the result of the injections. Special precautions should be taken if the patient has hæmorrhages, as in phthisis these have generally a toxic origin.

Lastly, there are the so-called skin reactions, characterized by definite and prolonged painfulness and inflammation at the site of injection. Their nature is quite analogous to the diagnostic needle-track or intracutaneous reaction²⁷ which has lately been recommended: they point to toxic tuberculin action and sensitiveness to tuberculin and therefore necessitate the same precautionary measures as the signs of reaction previously mentioned. This is shown by the fact that according to the degree in which the tox-immunity increases, these and all other toxic actions of the tuberculin generally disappear. The injections in treatment are not given intracutaneously but subcutaneously ;

**Focal
Reactions.
Hæmoptysis.**

**Skin
Reactions.**

sufficient tuberculin, however, leaks into the prick to give a skin reaction if the sensitiveness is great enough. Hamburger²³ states that the intracutaneous reactions he uses for diagnosis are quite the most sensitive tuberculin reactions, and this claim is very often borne out in treatment. However, if the effect of the tuberculin is to be correctly judged by these skin reactions, the place of injection must be taken into consideration.

Influenced by Site of Injection. Injections in the trunk are less likely to produce pain and inflammation than those in the extremities. If, then, a quantitative

estimate of the varying tuberculin sensitiveness is to be made by skin reactions, the injections must always be made in the same part of the body, say, in the thorax. It is evident that the injections must not be made each time in exactly the same spot, otherwise local summation reactions will be produced which will prove unpleasant for the patient. A little uneasiness at the site of injection, passing off in a few

Non-specific Skin Reactions. hours, is naturally not to be considered a skin reaction, as this may merely be caused by unspecific irritation of a small branch of a cutaneous nerve by the injection. True skin reactions are shown by a longer duration of the pain and by infiltration. It is, of course, self-evident that any lack of asepsis or the use of contaminated solutions will give rise to pain in the site of injection. Mistakes of this kind further add to the difficulty of estimating the tuberculin action and may do harm to the patient.

Experiments have been made recently in my clinic in the estimation of the leucocyte-content of the blood during tuberculin injections. Our results and those of other workers agree in showing that tuberculin reactions which take place in such a tuberculin treatment as I have

Leucocyte-content of Blood during Treatment.

described are generally accompanied by a rise in the number of leucocytes. Our experiments proved further that this leucocytic reaction is a finer test of toxic tuberculin action than other clinical phenomena. The neutrophile leucocyte count described by Arneth must also be mentioned, as it may have some clinical value; it seems to me however that without going into such minute details, a simple leucocyte count is one of the best and most exact methods of recognizing any signs of reaction in the course of treatment and regulating the dose accordingly. By the usual method of counting, employed in Germany, it is hardly possible to make a leucocyte count before each injection. A new and

**A New
Counting
Method.**

improved instrument has, however, been made by Leitz and Co. at my suggestion, which improves the Hayem-Nachet counting method;* by means of this instrument, an approximate count can be made in a few minutes, or, if necessary, an exact determination in quite a short time. The technique is as follows: An ungraduated leucocyte chamber is filled with the mixture to be counted; by means of an automatic movable stage, this is placed under a convenient micrometer eyepiece, which appears black to the eye and corresponds to a fixed area of the preparation. A glance at the leucocyte-content of a few such fields will give, by means of a table, an approximate leucocyte count; by increasing the number of fields observed, any required degree of accuracy can be quickly attained.

Now that we have described the toxic actions of tuberculin, and have shown how they are to be recognized, the reader ought not to meet with any special difficulties in correctly conducting a tuberculin cure, provided that the

**Possibility of
shortening
the Treatment.**

* Cf. my "Text-book of Clinical Methods," 6th Edition, 1911-12.

general rules for dosage are obeyed. Even the very slightest sign of a toxic tuberculin action demands the precautions we have mentioned as regards dosage and frequency of injections.

A course of treatment carried out in this way may certainly last a long time, as a simple calculation will show, for not only is the increase of dose very small, $\frac{1}{20}$ c.c., but, in addition, reactions sometimes occur in spite of every precaution and prolong the treatment. It must, however, be realized that one can often go through the weaker solutions with a quicker rise of dose, and, later on, a rise of a whole division is not infrequently admissible. As a rule, the therapeutically active dose is reached fairly quickly in favourable cases, which is the first aim of the treatment. The disease is then well on the way to cure as far as this is possible by means of tuberculin.

In connection with the duration of treatment and ultimate size of dose, a further important fact must be noticed. I have lately seen many cases in which the largest dose tolerated was not the therapeutic optimum, the latter being considerably smaller. This shows that in many cases one must find out not only the individual maximum, but also the individual optimum dose. These two doses are, then, not always the same; and I find that cases in my practice are ever increasing in which the therapeutic optimum dose is quite a small one—perhaps between $\frac{A}{34}$ and A; in these cases the repetition of these small doses is followed by such good results that there seems no need to increase them. This fact clearly illustrates the difference between the two schools of tuberculin therapists:—

(1) There are those who believe in a principle of real immunization as applied to tuberculin treatment, and

consider, therefore, that successful results with tuberculin can only be obtained with large, or even very large doses.

(2) In direct antithesis to this, there is the conception of an immunizing healing action which I have attempted to explain; this can sometimes be attained by quite small doses; and we must imagine that each one of these gives, to a certain degree, a small extra incentive to natural cure.

Those who agree with me in accepting this latter conception will realize how illogical is the standpoint taken by Dr. Landmann.²⁹ Arguing from the analogy of the preparation of a serum, he considers it necessary to reach as high toxic doses as possible, and states that, since his tuberculin is the most toxic of all tuberculins, it is therefore the best. It is a well-known fact that in the preparation of anti-tetanus serum, the animals become so weak with a kind of histogeneous hypersensitiveness to tetanus-toxin that if the toxin dose even slightly exceeds the antitoxin present, they are easily killed by tetanus. This, too, in spite of the fact that they provide an extremely active anti-tetanus serum. This is the best illustration of the fundamental difference between immunization and immunizing healing action, and between the manufacture of a serum and an active immunizing treatment. A human being is an egotist with regard to tuberculin treatment, but the serum-giving animal, on the other hand, is compelled to be an altruist for the sake of suffering humanity and often dies a martyr to the cause.

Two explanations suffice to explain the fact that better results are often obtained with smaller than with larger doses even when the latter are well tolerated:—

(1) The larger doses often produce undue tissue-damage.

(2) The production of antibodies, in the fullest sense of the word, is an irritative action and it is well-known that the effect of physiological irritation is not generally proportional to the strength of the stimulus, but rather chiefly depends on the condition of the organs in question: thus a weaker stimulus often produces a greater effect than a stronger one, since the latter may cause paralysis.

It can therefore easily be realized that, in an active immunization, the conditions may be such that a smaller quantity of toxin (the antigen) incites a better production of antitoxin than a larger quantity; besides, if the amount of toxin is large, a certain proportion of the antibody goes to neutralize it.

**The Balance
of Toxic
Action.**

This view is also confirmed in other branches of immunity such as the active immunization against enteric fever.³⁰ It must also be remembered that there is no constant proportion between the harm done by the tuberculin in promoting the irritative action and the favourable anti-actions; thus it sometimes happens that in high doses the harm done is not counterbalanced by the anti-action, as would be the case with small doses.

This question is not really so involved as it may seem at first sight, and to clear it up once and for all, I will recapitulate one section of the discussion on this subject with Landmann. He took up the position that the more toxic a tuberculin is the better, without even distinguishing between specific and non-specific toxicity of tuberculins. His argument is drawn from the manufacture of serum where, of course, a powerful toxin is used as antigen to produce a potent immune serum. Before discussing the logic of this conception, I will describe the exactly opposite view taken by Beraneck. He attempts to exclude from his tuberculin all excessively toxic substances, especially those of no immunizing value. The justification of this is borne out both by the experiments of the Pasteur school and the later research of Ehrlich, which proved that immunity and production of antibodies result from the injection of artificially weakened bacterial toxins as well as toxoids

and toxones. This is easily explained by Ehrlich's theory that the chemical structure of toxins, toxoids and toxones, is very similar or, as he himself puts it, that these three kinds of substances have corresponding haptophore groups. This fact is well known in immunity research and is of far-reaching practical importance. Ehrlich has shown, for example, that it is extremely difficult to immunize a mouse or guinea-pig to tetanus by unaltered tetanus-toxin owing to the great sensitiveness of these animals, immunity being easily obtained with a toxin weakened by means of carbon disulphide. Again, in the preparation of serum for the treatment of tetanus and diphtheria, immunity is easily obtained with a toxin weakened by iodine preparations. Now Beraneck has shown that he has diminished just the non-specific and therefore useless toxicity of his tuberculin; why, then, should not these substances, less toxic but none the less immunizing, be used in the treatment of tuberculosis, substances which Beraneck has been able to extract from tubercle-cultures by a method deviating somewhat from the usual routine?

I may say at once that I believe the ideal, at present a very long way off, lies in exactly the opposite direction. It seems to me that this ideal would be the treatment of infections by toxoid immunization, the stimulation of the immunizing anti-actions of the organism by substances of little or no toxicity. These specific toxoid-like substances should possess the same haptophore groups as the corresponding toxins, but should be as free as possible from the toxophore groups which characterize these toxins. It seems very improbable, however, that tuberculosis can be easily reached by these means; for in tuberculosis the toxic actions do not play the chief and decisive part as in other infections running an acute course. Therefore, an immunizing treatment only satisfies a section of the indications in this disease as, unfortunately, progress of the tuberculosis is often enough caused by purely constitutional weakness. This is clearly proved by the researches of Nägeli and Burckhardt (*loc. cit.*) who found that the great majority of cases of tuberculosis heal spontaneously and it is evident that only those do not in which there is some constitutional weakness. To avoid any misunderstanding, however, I must clearly state that Beraneck's tuberculin is unfortunately not a toxoid. It will be clearly shown in the Theoretical Part (p. 117) that tuberculin Beraneck has a high toxicity but, in distinction to other tuberculins, this toxicity is almost entirely specific.

One further question remains to be answered: after the individual or absolute maximum has been reached

<p>How long should the Maximum or Optimum Dose be continued?</p>	<p>and the optimum dose discovered, how long should the injections of the latter be continued?</p>
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It is clear that by the mere single injection of the absolute maximum dose, the problem of tuberculin treatment is not solved.* On the contrary, it is a question of maintaining the tox-immunity as long as possible and if circumstances permit, of raising it, and repeating the stimulation of the natural healing process as often as may be. This process, which always runs a slow course, is thus given time to do its work under the most favourable conditions.

We can say, therefore, that the treatment should be prolonged as long as possible, injecting either the largest dose reached without unfavourable results or the optimum dose which must first be discovered; at any rate, the injections should be continued as long as any improvement in the condition is seen. It is evident to anyone who has grasped the basis of tuberculin treatment that if for any reason the tolerance decreases, the dose must be reduced or the treatment suspended. It will also be

**Possibility of
Ultimate
Increase of
Dose.**

realized that in cases where the individual maximum or optimum reached is lower than the absolute maximum and the results of treatment are not entirely satisfactory, careful attempts may be made from time to time to increase the dose.

The fact that this increase is frequently possible after long-continued injection of the same dose and that good results are obtained by this means proves, as Denys has found, that prolonged treatment even with the same dose increases tox-immunity, each fresh injection providing a new stimulus to the production of antibodies.

*The view held in the 'nineties is still occasionally met with that cure of a case of tuberculosis may be assumed when no symptoms are present and the patient no longer reacts to the largest doses of tuberculin. This is, however, not borne out in practice and the fact is overlooked that many other factors besides general tox-immunity are necessary for the cure of tuberculosis.

There is a great difference in principle between this continued repetition of the maximum or optimum dose and the interrupted or serial treatment recommended by Petruschky after the maximum dose is reached and tolerated.

**Petruschky's
"Serial
treatment."**

The difference of method undoubtedly depends on a different theoretical view of the matter. Petruschky's method is bound up with the conception that manifest reactions are essential and have a curative significance, since he considers it useless to prolong the treatment after the cessation of reactions. According to my conception, tuberculin treatment is primarily concerned with the production of antibodies accompanying tox-immunity, and secondly, of course with the promotion of a reactive influence on the tuberculous organs; but this must take place in the silent workshop of nature and is only harmless and desirable when incapable of clinical recognition.

If the course of treatment is to be prolonged, it can be very much lightened for both practitioner and patient

Longer intervals between the Largest Doses. by giving the high doses at longer intervals (cf. p. 52), for instance injecting the absolute maximum but once a fortnight. Experience shows that these large doses have a

powerful and lasting action; therefore, in spite of the long intervals, the tox-immunity is not merely maintained but even increased and the stimulation is quite sufficient to promote a natural cure. There are many patients who have done so well that they feel inclined to discontinue treatment altogether; these can be much more easily persuaded to receive fortnightly injections for a few months, than to continue as before, twice a week. This lengthening of the interval further prevents any chronic surcharge of toxin which might otherwise

occur with large doses, a point emphasized by Denys in his technique. On the other hand, the interval should not be increased if only a low individual maximum or optimum dose has been reached, a dose, for instance, from solution C or even a still weaker one.

In spite of the fact that the therapeutic results of the tuberculin can often be recognized very quickly, a correct
Treatment should be continued as long as possible. tuberculin cure, aiming at the highest ideal, generally requires a much longer time to carry out and the patient should be made aware of this at the start. In the earlier

edition of this book, I have stated that unless the patient can spare at any rate a few months, it is not worth while commencing treatment. Since then I have seen many cases in which a few week's treatment—in some very slight cases, even a few injections—has very considerably improved the condition or even brought about a cure: therefore, lest any possible benefits of tuberculin treatment should be lost, I no longer maintain this opinion but am inclined to recommend that even if there be but a short time at the patient's disposal, if the indications are favourable and especially if the case is an early one, the treatment should be commenced. However, the fact remains that tuberculin treatment is

Tuberculin the concern of the Family Doctor.

not generally complete in a few weeks and even when a rapid improvement is made, it ought later to be repeated: it is clear, therefore, that tuberculin treatment must be the business of the family doctor if its full benefits are to be obtained: if the treatment is only carried out in hospitals and sanatoria, the patient either is likely to be treated too hastily or else gives up the treatment too soon. The latter point has always been a source of trouble with my hospital patients. If once the general

practitioner can acquire the correct knowledge of the subject, it will be found that home treatment is all the easier to carry out in practice, since the tuberculin cure by no means prevents the patient from following his profession or business, unless already bedridden. The adoption of tuberculin treatment by the general practitioner has the further advantage that he and he alone is able to prescribe the treatment for the quite early cases, in which the prospects of success are greatest.

Although it is not generally advisable to discontinue treatment if satisfactory progress is made with the graduated dosage, yet a temporary break has no very serious drawbacks if circumstance demands it; the practitioner in charge of the case may be absent for a time or the patient may have the opportunity for a stay in the mountains. During such a break, the earlier sensitiveness to tuberculin often gradually returns; the cure must therefore be recommenced very carefully, the sensitiveness tested with the smallest doses and in any case a much smaller initial dose given, to be decided by cautious trial. After any considerable break in treatment, the cure must never be recommenced with the same dose that was tolerated before the cure was suspended.

**Temporary
breaks in
Treatment;
their
Significance.**

Of the cases favourably influenced by tuberculin treatment, complete cure is unfortunately only obtained in a small section, the earlier ones. All that can be obtained in many cases is what I have called compensation of the tuberculosis, the establishment of a kind of balance between disease and organism, a truce between the tubercle-bacilli and tuberculous tissues or the cessation of active phenomena.

**Results of
Treatment in
Severe cases:
Compensation.**

By the occurrence of this condition, the chronic affections are distinguished from the acute. The word symbiosis, formerly used by me to describe it, is not quite correct, as by symbiosis one understands the living together of organisms of different natures, each using the other to advantage. This is not the case here. At least, it is not clear at first sight that an inactive tubercular focus can serve any useful purpose for the patient in question; yet as a matter of fact, there is some ground for the assumption (p. 161) that such an inactive focus may to a certain extent protect the patient from the formation of the new foci, and thus from fresh infection by dissemination of the tubercle-bacilli. If, however, the resistance of the organism decreases at any time, this protection fails.

This condition which is often reached spontaneously in tuberculosis is of great practical importance; such patients, even with quite extensive tuberculous changes, often reach a very old age without troublesome symptoms and, as every doctor knows, such extensive but inactive processes are frequently discovered quite accidentally in examining old people who considered themselves quite sound and even boasted of their strong lungs. The term cicatrization, often used to describe such a condition, is often quite an incorrect euphemism as autopsies will show.*

In a third category of cases, a certain amount of improvement is made, but such definite signs of disease remain that one cannot speak of a compensation or balance but only of the slackening down of a process which is still progressive. Lastly, there are cases in which the excessive sensitiveness to the toxin or the already existing surcharge of it renders any chance of success with tuberculin treatment impossible. However, it must not be imagined that all high sensitiveness is in

Results in the
worst cases.

* Practitioners who see but few autopsies often misuse the words "cicatrization" and "cicatrix." It is impossible clinically to distinguish between tuberculous scars and inactive "compensated" infiltration.

itself a hindrance or even a drawback to tuberculin treatment (cf. p. 180); on the contrary, these cases are often quite suitable for treatment by small doses. Only those cases are really unsuitable for tuberculin treatment in which this excessive sensitiveness does not diminish during treatment in consequence of the production of antibodies.

If no further improvement seems to result in spite of prolonged treatment or if the tuberculin seems to do no good after a very careful trial, one should not be too easily persuaded to give up the cure provided that absolutely no harm is resulting from it. A patient continuation of treatment often meets with success, even after many months. This is, however, only admissible if the patient is, at any rate, none the worse for the tuberculin. There, the possibility of an extraordinarily slow and almost imperceptible action has to be taken into account. A previously unsuccessful tuberculin cure might perhaps be repeated after an interval of say six months and such repetition is suggested by the well-known fact that, owing to constitutional changes, the action of the same curative agent may vary considerably at different times; thus tuberculin which proved inert at the first trial may, at the second, prove active. Purely hygienic-dietetic methods of treatment, a rest cure or stay in the mountains may change the whole aspect of a tuberculin cure.

If the results of treatment are favourable and if, after injections lasting for some long period, the cure is maintained for several weeks or months, the treatment should be temporarily suspended. The question will arise, however, as to whether and after how long an interval, the cure should be repeated? This is naturally indicated

**How to deal
with Initial
Failure.**

**Repetition of
Treatment.**

when, after a prolonged period of satisfactory general condition, signs of the old trouble reappear or are increased, and this sometimes occurs quite soon after the problem has been considered solved. It is more difficult to decide whether to repeat the treatment as a prophylactic measure when all seems to remain quite satisfactory. However, two considerations point to a repetition:—

(1) The deceptive nature of the disease which may simulate cure while the fire still smoulders under the ashes (*cf.* p. 74) and

(2) The experience that tox-immunity gradually decreases. One should always be prepared for relapses, as no lasting or complete immunity is secured by tuberculin.

It is difficult to decide after how long the tuberculin cure should be repeated and it seems hardly possible to lay down any definite rules for this.

Return of Sensitiveness. According to the researches of Petruschky, after reaching complete tox-immunity to the largest therapeutic doses of Koch's old tuberculin, sensitiveness returned in about three months:

on this fact, he bases his serial treatment in which he allows an interval of three or four months

Petruschky. to elapse after maximum tox-immunity is attained and then recommences treatment; thus his treatment generally lasts about two

years and consists of four periods of injections of two to three months and as many of rest of three to four months.

Denys has found that with his tuberculin and using his method of treatment, maximum tox-immunity lasts much

Denys. longer: in three tests, five, twelve, and nineteen months respectively. It must be admitted that the difference in potency alone of the two tuberculins partly explains the

varying estimates; in addition, the longer duration of tox-immunity found by Denys is accounted for by the fact that his treatment is more gradual and lasts longer than Petruschky's. The individuality of the patient must also further influence the duration of tox-immunity. Thus the conditions are so complicated that no general statement can be made of the exact point of time at which a successful tuberculin cure should be repeated. The interval can be roughly estimated at a few months. No systematic experiments have yet been made in this direction specially for Beraneck's tuberculin, but individual variations would render these of little value. Thus, as in all departments of medicine, much is left to what has been wrongly called the practical judgment of the doctor, better expressed as clinical common sense and, in no small measure, to external considerations. The guiding principle, however, as in tuberculin treatment in general, is the conception that tuberculin is unfortunately not a true specific but a means of influencing quite a definite function of the body—its sensitiveness to toxin and its power of resistance. Similarly, digitalis exerts an influence on the heart-beat without a specific influence on any definite cardiac disease.

SUITABILITY OF VARIOUS TUBERCULOUS CONDITIONS FOR TUBERCULIN TREATMENT.

The general method of treatment described is suitable for all localizations of tuberculosis, since the process of infection and cure is, in principle, the same in all the many forms of the disease. Thus I have obtained successful results (especially with Beraneck's tuberculin) not only in pulmonary tuberculosis, but also in tuberculosis of the serous membranes (tuberculous peritonitis and pleurisy), of the larynx, of the urinary tract and kidneys,

of the intestines, of the brain, of the skin and glands, and in a few other cases of surgical tuberculosis.

I should like to draw special attention to the fact that in cases of tuberculosis of the bladder and kidney which are not too far advanced, the tubercle-bacilli have disappeared and a clinical cure been brought about. It does not therefore seem

**Tuberculosis
of the Urinary
Tract.**

necessary to adopt the radical measure of extirpation of the kidney in every case of renal tuberculosis. Everything depends, however, on the early diagnosis of the disease and if, in recommending tuberculin treatment for slight initial cases of renal tuberculosis, I am in opposition to the general views on the subject, I wish to make it perfectly plain that really bad cases with extensive suppuration are no longer suitable for

**Early Diagno-
sis necessary.
Significance
of Bacilluria
and Albu-
minuria.**

tuberculin treatment, but must be operated upon. Nevertheless, progress in the treatment of this disease does not, as some assert, rest merely with operative treatment, particularly not with early operation; it depends rather on greater care being taken in an early diagnosis of the condition at a time when a cure is possible without operation. With this object in view, special attention should be paid:—

(1) To the bacilluria so common in women and often running a latent course; and

(2) To albuminuria which is the first sign in so many cases of tuberculosis of the kidney. In every case of albuminuria, the urine should be examined for tubercle-bacilli.

Solitary cerebral tubercles are very suitable for tuberculin treatment, the more since spontaneous cure or at least stasis of this disease frequently takes place, and the prognosis of operative treatment is not very good owing to the indistinct limits of the foci and their multiple

**Cerebral
Tubercle.**

occurrence, and also on account of the danger of operative tuberculous meningitis.

Cases of tubercular spondylitis have also given very favourable results. Of course, in addition to the tuberculin treatment, other indications, especially for immobility, extension, &c., must not be neglected.

**Tubercular
Spondylitis.**

Ophthalmic physicians have had very good results in those tubercular diseases of the eye⁸¹ which recent experience has shown are so frequently disguised under slowly progressing uveitis. I myself have to chronicle striking success in two cases of severe phlyctenular or scrofulous condition of the eye which had previously withstood all other methods of treatment. I would, therefore, strongly recommend a trial of tuberculin treatment in similar conditions. The cases mentioned have led me to think

**Ocular
Tuberculosis.**

Tuberculides.

that these affections might possibly have a similar origin to the tuberculides of dermatology. I agree with Wolff-Eisner that these tuberculides are inflammatory reactions to tubercle-bacilli carried to the spot by the circulation; probably owing to strong allergic reactivity or hypersensitiveness of the organism, they do not produce actual tubercles nor are the bacilli increased to any great extent but only inflammatory reaction phenomena are seen (*cf.* p. 159). Even if, in accord with modern ideas of the nature of scrofula, one considers these so-called scrofulous diseases of the eye simply as signs of hypersensitiveness to the tuberculin content of the tissue juices (*cf.* p. 166), the successful results mentioned are quite intelligible and the use of tuberculin in similar cases indicated.

Tuberculin is also indicated in scrofulous eczema of

the skin (*cf.* pp. 164-169) and I call to mind one very striking case in which tuberculin produced a remarkable and rapid cure.

**Scrofulous
Eczema.**

Lastly, I have treated a large number of cases during late years of arthritis with deformity of the phalangeal

and other joints in which there were pronounced signs of latent pulmonary tuberculosis. I have, therefore, come to the conclusion that this arthritis has a similar

Arthritis.

significance and origin to tuberculides of the skin; tubercle-bacilli are carried by the blood-stream to the joints, which display a special predisposition, but allergia or hypersensitiveness prevents the development of ordinary tuberculosis of the bones or joints and merely chronic inflammation is set up. These cases are therefore very suitable for tuberculin treatment.

The extension of tuberculin treatment to these cases, the nature of which is at present obscure, should meet with

great success and extend our pathological knowledge of the various conditions. I feel convinced that many doubtful affections of internal organs, many painful abdominal

**Many other
Affections to
be considered
as Tubercular.**

troubles and even the so-called chronic appendicitis are often to be regarded as tuberculides in a broad sense of the word and should be treated accordingly.

Although in all localizations of tuberculosis there is hope for a successful tuberculin cure, it is clear that by

no means all cases of tuberculosis are suitable for treatment. This is not a question of localization but of the nature of the

**Unsuitability
of very
Acute Cases.**

tuberculous process or, as we generally say, of the acuteness or virulence of the case in point. This can easily be understood, as the more prominent the signs of intoxication or overloading with toxin, the less

can be expected from tuberculin treatment. The acuter the symptoms in a given case, the less is it suited to the theory and, as experience shows, the practice of tuberculin treatment.

It is, however, not quite correct to argue from this rule that the miliary forms of tuberculosis must as such be excluded from tuberculin treatment. It is just in tubercular meningitis that it is quite common to find scanty tubercles in the fossa of Sylvius, and the general phenomena of intoxication are often quite slight, there being frequently little or no fever. It seems possible that the development of the disease could sometimes be cut short by early tuberculin treatment, especially when one thinks of lysin-action on the tubercle-bacilli themselves (*cf.* pp. 160 and 178). The initial number of tubercle-bacilli is small and possibly for this very reason this bacteriotropic lysin-action does not increase the danger of intoxication, even when it does not merely weaken the tubercle-bacilli but also to a large extent dissolves the bacillary substance. This action would also extend to the free tubercle-bacilli almost always found in the cerebro-spinal fluid, which probably help to spread the disease in cases not combined with general miliary tuberculosis, and this not by means of the blood but by the cerebro-spinal fluid. It must also be noticed that miliary tubercle, especially of the peritoneum, as is so often discovered in laparotomies, may disappear extraordinarily easily; and that the bacteriolytic and antitoxic actions in tubercular meningitis may count much more than in compact foci, since the free bacilli and the miliary tubercle are in direct contact with the fluid into which the antibodies can easily pass. Thus the mechanical difficulties in the way of antitoxic action are very much smaller than is the case with larger

**Treatment of
Miliary Tuberculosis.
Tubercular
Meningitis.**

internal foci, owing to the non-vascularity of the latter (*cf.* p. 14). The prognosis in tubercular meningitis is almost hopeless, and for this reason if for no other, tuberculin treatment should be tried, an experiment I intend to make at the first opportunity.

The conditions are much more unfavourable in general miliary tuberculosis and the tubercle septicæmia which has recently been described,³² as the danger of bacteriolytic intoxication by bacillary protein due to the tuberculinolysin is much greater on account of the large number of tubercle-bacilli present. This danger is further increased by the powerful toxic action already at work in many cases. In spite of the unfavourable prognosis in these conditions, it would seem admissible to try tuberculin treatment in cases, necessarily few, where an early diagnosis can be made.

If the question is asked "What prospects are held out by tuberculin treatment in the various forms of tuberculosis?" the answer must clearly be that the earlier the diagnosis and treatment the better will be the results. We must therefore consider the

IMPORTANCE AND METHODS OF EARLY DIAGNOSIS.

Too great stress cannot be laid on the fact that a large number of cases of pulmonary tuberculosis are not diagnosed at an early stage, and not, as a rule, because diagnosis is impossible but because the patients either do not complain at all or else ascribe their symptoms to anything but lung trouble. In the first case they do not visit a doctor and in the second they are often not sufficiently carefully examined as to the condition of their lungs and are wrongly diagnosed and treated often

**Unfavourable
Conditions
in General
Miliary
Tuberculosis.**

**Necessity for
Accurate
and Early
Diagnosis.**

for years for neurasthenia, stomach trouble or anæmia. I will not speak of the careless mistakes in diagnosing and treating anæmia without proving its presence by examination of the blood; but no small percentage of the cases in which anæmia is definitely proved is to be laid to the charge of latent tuberculosis. In this case, treatment for pure anæmia will be of little use. These errors in diagnosis often depend on too superficial an examination of patients and also on the fact, still too little known, that early tuberculosis is, in respect of clinical signs, a veritable proteus, so often clothed in the guise of neurasthenia, stomach complaints, chlorosis or other affections.*

I think, too, that these early cases of pulmonary tuberculosis would be less frequently overlooked if the significance of Nägeli and Burckhardt's experiments³³ were understood and the frequency of anatomical tuberculosis fully realized. Their statistics and the frequency of positive von Pirquet cutaneous tests in adults show that practically every adult person carries tuberculosis about with him as well as original sin. Although of course the figures of Nägeli and Burckhardt refer generally to anatomical conditions of no considerable magnitude, yet it cannot be assumed that these have always been completely latent. If these considerations were borne in mind we should be less easily satisfied with the unsatisfactory and unscientific diagnosis of influenza in most cases of persistent chronic catarrh. The possibility of tuberculosis would more often be considered, even

* I have even seen gastro-enterostomy performed on cases of pulmonary tuberculosis on account of gastric symptoms, and the appendix removed because of radiating pleuritic pain, without the trouble having been taken to examine the patients thoroughly.
"Difficile est satiram non scribere!"

when the signs disappear. Such a patient would be kept under observation and frequently examined, and thus many an early diagnosis of tuberculosis made and tuberculin recommended, when without this diagnosis he would go about for years without taking any care of himself, sometimes until it is too late for treatment.

A practitioner who is acquainted with the enormous frequency of tuberculosis and who repeatedly and carefully examines his patients can sometimes diagnose a case of pulmonary tuberculosis years before a fellow-physician, without possessing any abnormal clinical skill. What this would mean in treatment is obvious. I do not intend to go into the diagnosis of early tuberculosis in any detail, but will only point out that in addition to frequent examinations of the lungs (not only the apices) and the sputum, correctly performed and frequently repeated measurements of temperature* should be made, even in cases where there is little ground for suspicion. One ought never to be satisfied with the patients' statement that they have no fever. As a rule, they cannot themselves tell. The record should be shown to the practitioner, who alone can settle the question of whether the patient is febrile or afebrile. Unusual variations during a day or longer period must be regarded as fever, even if the highest point reached is below the fever point as commonly understood.† By this means the conscientious and skilful practitioner will be able to diagnose many cases of early phthisis, which can be dealt with by tuberculin treatment.

**Temperature
as a Guide to
Diagnosis.**

* Cf. p. 58.

† A description of the diagnosis of fever and the conception of relative fever will be found in my "Text-book of Clinical Methods" (6th edition, F. Deuticke, Vienna).

(I consider the early diagnosis of tuberculosis of the greatest importance, and am convinced of the value of tuberculin treatment, but am absolutely opposed to diagnostic tuberculin injections.)

Diagnostic Tuberculin Injections not justified. In the Theoretical Part (p. 144) it will be seen that Wolff-Eisner has collected evidence which goes to prove that no definite conclusions can be drawn from either a negative or positive result of the so-called diagnostic injections; apart from this fact, I consider the risk attending their use sufficient argument for their rejection. Indeed, how illogical it would be to advise the exposure of patients to the danger of overloading with toxin merely for diagnosis, after having emphasized the fact that tuberculin treatment is only harmless when the greatest care is taken in dosage and all reactions avoided. In the diagnostic use of tuberculin, one is aiming at the very thing that is known to be dangerous—overcharging the body with toxin to make it react, and if this is not successful the first time, a second and third attempt is made, often with a dose many times as big again! This does not seem admissible in the treatment of human beings: the result is not even conclusive, and the measure almost always superfluous.

The modern harmless methods of using tuberculin for diagnosis: the cutaneous, intracutaneous, percutaneous (ointment) and conjunctival reactions, have unfortunately proved of such little value that they are not of much use in early diagnosis (*cf.* p. 146). Only for children under four years of age does von Pirquet's cutaneous reaction form any serviceable criterion for diagnosis, as at this time of life any tuberculosis present is, in the great majority of cases, active and thus of clinical

Local Tuberculin Reactions.

significance. } With increasing age, the statistics of Nägeli and Burckhardt show that, in addition to the tuberculosis clinically observed, there is an increasing amount of rudimentary tuberculosis which has become inactive and healed; this latter is of no clinical significance, but nevertheless produces a positive cutaneous reaction. The conjunctival reaction is still considered by Wolff-Eisner of use in the diagnosis of active tuberculosis, provided that the test is not repeated; its value in diagnosis is, however, greatly disputed by other authorities, and personally I cannot feel justified in using such an important organ as the eye for these diagnostic experiments, since, neither in theory nor practice, is it possible to be sure of avoiding harmful or at any rate unpleasant results.

The new so-called specific methods of diagnosis, such as agglutination, complement-fixation, activation of cobra-toxin, and opsonic estimations, have proved in general of little practical value, and I do not think that they will materially add to the possibility of early diagnosis.

**Failure of
Specific
Methods of
Diagnosis.**

A modification of the cutaneous reaction, using graduated tuberculin dilutions ($\frac{1}{10}$, $\frac{1}{100}$, $\frac{1}{1000}$ of Koch's old tuberculin) has been used with success for a long time in my clinic, and seems of much greater value. If a positive result is obtained with a $\frac{1}{1000}$ dilution, we make further tests with dilutions of $\frac{1}{10000}$ and $\frac{1}{100000}$.^{*} Both this method and also the graduated intracutaneous reaction † described by Hamburger,³⁴ and lately used for cattle by Römer,³⁵ will possibly prove to be of real help

**A Modified
Cutaneous
Reaction.**

^{*} We have lately used dilutions of concentrated tuberculin Beraneck in the same way.

† The injection of the smallest quantities of Koch's tuberculin, causing no general reactions, into the skin, not under it.

in diagnosis by showing the exact quantitative capacity for reaction, although they will probably not afford definite proofs of the presence or absence of active disease. These methods have not, however, been sufficiently employed to admit of any definite statement of their value.

Apart from these modern methods, the early diagnosis of tuberculosis is not of any great difficulty for the practitioner who bears in mind the many-sided nature of the disease considers hereditary influence, and is well up in the enormous frequency of tuberculosis. It must be admitted, however, that it is often very difficult to make a certain and definite diagnosis in early cases, in which tubercle-bacilli are frequently not present in the sputum. One of the greatest advantages of tuberculin treatment in the form here outlined is that by cautious dosage it is so entirely free from danger that it may be conscientiously recommended when the diagnosis of tuberculosis is only a probable one, when the disease is only suspected and as a prophylactic measure for those in danger of infection.

**Clues to
Diagnosis
from First
Doses.**

Although diagnostic tuberculin injections are not justifiable, yet it should be remembered that observation of the effects of the first few therapeutic injections may be of great value in diagnosis. The slight signs of reaction, which cannot always be entirely avoided in treatment, confirm the diagnosis just as much as do intentional tuberculin reactions; indeed, the proof is still stronger, as they are the result of much smaller doses. Thus the treatment itself may be of value in diagnosis, and even if for this purpose somewhat larger initial doses are given, a thing that I by no means recommend, this would be a mild and harmless method of diagnosis compared with

the violent and dangerous diagnostic tuberculin injections.

RESULTS OF GENERAL TUBERCULIN TREATMENT.

In the preceding pages we have seen the necessity for early diagnosis, and that even when this is not certain and definite, a more or less prophylactic cure should be commenced. By these means, an extraordinary amount of good may be done and it is to such cases that the statement applies that tuberculin treatment is destined to play just as valuable a part as vaccination in the fight against smallpox. Initial cases, especially if afebrile, are often improved or cured in quite a short time. The first things to be noticed are generally the improvement of the general condition, increased appetite and weight and a more healthy appearance: the signs of local healing soon follow—decrease of sputum and cough, disappearance of râles and dullness, reduction in size of tuberculous glands and so on. All this can often be attained without any change in the patient's mode of life. Knowing this and considering the much less favourable results of tuberculin treatment in bad cases, it seems difficult to understand why early cases are so often dissuaded from tuberculin treatment with the assurance that it is not necessary for them. On the other hand, one often sees tuberculin treatment being given in severe cases, in which the prospects of success are very small, with patience and energy worthy of a better cause, but without notice being taken of the harm done by it. This clearly shows the lack of any fixed conception of the therapeutic action of tuberculin.

First Signs of Improvement.

Tuberculin especially valuable for slight Cases.

Such a standpoint also probably depends on an

insufficient knowledge of correct technique, the practitioner not having got rid of the idea that tuberculin treatment is two-edged and somewhat dangerous and therefore naturally having some compunction about employing it in slight cases. I should like most firmly to protest against the withholding of tuberculin treatment from slight cases where it can work wonders and its application in severe cases, *solaminis causa ut fiat aliquid*. The treatment is of too active a nature to be used as a mere *solamen* and nothing does so much to prejudice general opinion against tuberculin as incorrect views of this kind.

The results are, of course, less favourable in these early cases when they are already febrile. As a rule, one should await the spontaneous defervescence of fever, prescribing rest, reduction of diet and salicyl treatment and only try tuberculin during fever when it is found that this spontaneous defervescence does not take place.

**Fever should
be allowed
to subside
Spontaneously.**

The significance and value of a reduced diet, of a short fasting-cure as a remedy for acute febrile phenomena, is still too little known, overfeeding being so largely recommended. Fever of all kinds, including the acute exacerbations of tuberculosis, often far more quickly subsides with a scanty than with a free diet; the reason for this is not yet fully understood, but of the fact itself, which found expression in the fever diet of ancient physicians, there can be no doubt. It is hardly to be explained by the simple idea that the bacteria are so to speak starved out: the most likely state of affairs is this—that on account of the incomplete digestion generally if not always accompanying fever, a very rich supply of nutrition from the intestinal tract brings new toxic factors into the question and perhaps even promotes the direct absorption of bacteria and foreign protein from the intestine. It is also probable that the decreased food supply acts as a direct antipyretic by diminishing the production of heat. It may, too, be possible that in excessive nutrition similar tissue-damage is caused by surcharge with nutriment as in diabetes by a surcharge of sugar,

The Diet.

and that by reducing the diet the tissues are so to speak relieved and more easily able to provide a supply of antibodies. A further analogy is seen in the dietetic treatment of chronic nephritis by diminishing the food. Again and again I have been convinced of the fact that the success of the treatment of tuberculosis is diminished by what is commonly called over-feeding. It seems to me that hypernutrition has a pathological significance and much harm may be done by it, although of course a sufficient amount of nourishment, adapted to the digestive power, is of the greatest value in treatment. Unfortunately, without medical advice, over-feeding in everyday life is only too common and it is one of the chief causes of many stomachic and intestinal complaints, including appendicitis. Even a temporary decrease of diet can do much in relieving fever, and this is especially true of phthisical patients who have previously been overfed. There is no greater delusion than to imagine that always and under all circumstances the patient should be compelled to put on weight. Many times I have seen patients increasing quickly in weight but getting worse instead of better. Increased weight in tuberculosis is of no value when it is obtained by "stuffing," but only when it is the result of an increased appetite and an improvement in the condition. In the latter case, the weight will go up of its own accord, often with quite a low caloric value of the food. It is to be noticed that thin men who do not eat a great deal are often not only healthier and longer lived than big eaters, but also exhibit a striking resistance to tubercular infection.

The temporarily reduced diet for febrile patients should naturally only last a few days, during which time it must be decided whether any good is done. If it has a favourable result and the fever subsides, the organism often shows an increased capacity for assimilation of a normal diet just as in convalescence from acute disorders; the tissues frequently absorb nutriment like a sponge, and I have seen many tubercular patients put on weight under these conditions with quite a restricted diet, patients whose tissues had previously refused the forced nutrition which gave rise to unpleasant symptoms. A short fast has an immediate rejuvenating influence both on the sound and the unsound. Besides this actual short fast indicated in acute exacerbations, permanent moderation in diet and forbearance from "stuffing" are most strongly to be recommended as a general *régime* for both febrile and afebrile cases. Many patients, especially the phthisical, often prompted by their doctors, are nourished on absolutely false principles, quite opposed to the laws of Nature, principles which are passed from one to another and induce them to put all their trust in weight records. For the phthisical and, indeed, perhaps still more for the sound, intemperance in eating causes serious damage to almost all the organs of the body.

In these cases where fever does not subside spontaneously, I commence treatment with extremely small doses, using solution $\frac{A}{256}$ or $\frac{A}{512}$. It often

**Treatment of
Febrile Cases.**

happens that with quite minimal doses the fever abates and finally disappears, after which the cases are just as favourable for further tuberculin treatment as those afebrile from the start. Such a defervescence of fever under tuberculin action seems striking if it is assumed that the fever in these patients is, so to speak, a spontaneous tuberculin reaction. The successful result of the injections, however, rather contradicts this conception and leads one to think that this

**Cause of
Fever.**

fever is not really a tuberculin action, but may, for instance, be the result of an albumose action³⁶ caused by the absorption of disintegrated tissue-elements. With this explanation, it is clear that in spite of the fever, just as in afebrile cases, the injections introduce into the morbid processes a new factor which acts as a curative agent. But even if it be admitted that the fever is a tuberculin fever, a favourable result of the injections is not absolutely unintelligible: it must then be assumed that the sudden variation in the concentration of the toxin in the organism, resulting from the injection, is the cause of the favourable anti-action, an anti-action which does not result from the more uniform toxin absorption in the natural course of the disease.

**Graduation of
Dose in
Febrile Cases.**

The rules for graduation of dose in these febrile cases are the same as in afebrile cases, the only difference in treatment being that the initial dose is much smaller. Here too the dosage must be so regulated that as far as possible all perceptible harm to the organism evidenced by rise of temperature, disturbance of the general

condition and skin-reactions, is avoided. It is, of course, quite natural to find after a time that in these febrile cases the tuberculin is not sufficiently tolerated by some patients, and, after a careful attempt at treatment, one is often compelled either to give it up or to await a more favourable phase in the disease.

Still more unsatisfactory are the results when the physical signs are very severe, a condition which is some-

Unfavourable Results in Severe Local Conditions, times discovered at the first examination of patients who have previously had no knowledge of their disease. Here, too, afebrile

cases are more favourable than febrile ones, and as a rule tuberculin treatment is of no avail for severe local conditions of the lungs accompanied by fever. This is probably because the body is already

owing to Sur-charge of Toxin. Non-reactivity. much overloaded with tuberculin and the condition is aggravated rather than improved by the injections. This state of affairs is

often betrayed by the fact that, in spite of the serious condition, even large doses of tuberculin cause no particular indisposition, no fever, no local reactions in the diseased part, no skin or other reactions. The organism may be already suffering so intensely from the toxin absorbed from the tubercular foci that the small addition in the injection does not essentially change the situation. A further reason may be given for the non-reactivity of severe cases: the lysin, which otherwise breaks down the tuberculin into highly toxic substances and causes focal, skin and general reactions, is completely used up (*cf.* Theoretical Part). This apparently low sensitiveness to tuberculin in severe cases, shown by the absence of the conjunctival and other local tests,* is then a definitely unfavourable

* *Cf.* pp. 145-146.

sign and by no means invites the continuation of tuberculin treatment. I am laying special emphasis on this point as, time after time, enthusiastic champions of tuberculin who do not recognize this *malum signum*, are deceived by such cases and unhesitatingly continue the injections because they perceive no reactions and therefore assume a good tolerance, while in reality a maximum surcharge of tuberculin is present. With care, however, it is quite easy to distinguish such cases from those in which the absence of reactions is the favourable sign of a really low sensitiveness to the toxin. It must then be remembered that an apparently low sensitiveness is often found in severe cases; and the harmful results of the tuberculin may easily be realized if they are not sought for in tuberculin reactions as generally understood, but in the general condition of the patient. In such cases, it will be found that under the influence of tuberculin the patient does not improve but rather continues to get worse. A high pulse-rate remaining

**Signs of Toxic
Surcharge.**

high or getting still higher during the injections and progressive loss of weight are characteristic of such cases. In a few cases of this category, I have also noticed the following phenomenon: general and focal reactions to the tuberculin have been absent because of the already existing surcharge of tuberculin or the insufficient supply of lytic antibodies, but skin-reactions have taken place, because the tuberculin injected acts on the skin in such concentration that its very quantity causes the reaction (*i.e.*, produces lytic actions) in spite of the general surcharge of toxin. In such severe cases, one

**Significance
of Reduced
Temperature.**

should not be deceived by the fact that the fever subsides during treatment. This is no proof whatever of the efficacy of the

tuberculin unless other unmistakable signs of improvement follow. I have often observed such a fall of temperature and, contrary to some doctors who consider it the sign of favourable tuberculin action, am not always so pleased to see it in severe phthisis; and results have shown that the opinion was justified. These cases often survive but a few weeks in spite of the assumed favourable action of the tuberculin on the fever. It should be remembered that in some cases of tuberculosis, the fever subsides quite spontaneously the last few weeks or months before death. Every experienced physician knows that this cessation of fever, unaccompanied by other improvements, is by

no means always a favourable sign. The
theory of fever ascribes this fall of tempera-
Cause. ture during the last few weeks of life to a
limiting of metabolic processes and heat
production; it is well known, too, that excessive doses
of bacterial protein produce not a rise but a fall of tem-
perature. If, then, such a drop of temperature occurs
as a clear and definite result of the injections and is
unaccompanied by other signs of improvement (increased
appetite and weight, &c.), one may quite well assume
that the tuberculin is not doing good but harm. A
clinically trained eye can, then, readily distinguish
between:—

(1) Fall of temperature accompanied by improvement of the general condition which is attained by tuberculin treatment in slight cases, and

(2) Fall of temperature in severe cases with the persistence or aggravation of the other symptoms such as high pulse-rate, which more sober judgment recognizes as an unfavourable sign.

I have specially emphasized the possibility of an unfavourable significance of a fall of temperature, since

tuberculin enthusiasts are so frequently deceived by it. In short, it is often a distinct token of intoxication, analogous to the frequent temporary falls of temperature during the injection of large doses of insufficiently tested sera, erroneously considered a favourable phenomenon. Not too much should be expected from the action of tuberculin on severe and advanced cases, be they febrile or afebrile.

**Deceptive
Nature.**

**Mixed
Infections.**

**Causes of
Failure of
Tuberculin
Treatment.**

A last category of cases deserves mention in which in addition to the primary tubercular infection, there exists a so-called mixed infection by pneumococci, staphylococci, &c. The significance of the latter with regard to tuberculin treatment is, in my opinion, overestimated. The many failures of tuberculin are not to be denied, but there seems no reason for continually ascribing them to these mixed infections, which are so often made the scapegoat for the imperfections of the treatment. I think it has been clearly shown that the majority of non-successes are due to the application of tuberculin treatment :—

(1) To cases in which, on account of their severity or some other ground, neither tox-immunity nor the graduated irritative actions essential for cure can be produced, or

(2) To cases in which the natural healing factors, also essential for cure, are absent.

A large number of the failures, however, are due to an incorrect technique resulting from an incorrect theory of tuberculin action. That severe cases are sometimes accompanied by mixed infection is well known, and this complication is unfavourable for tuberculin or any

other treatment. Severe cases even without mixed infection can often no longer be influenced by tuberculin treatment: but, on the other hand, tuberculin may have a favourable result in cases with mixed infection if the conditions are not too unfavourable, by exerting an influence on one of the two components of the morbid process, the tuberculosis having its influence on the mixed infection and *vice versa*. One thing is certainly clear and that is, that the local tissue-damage in the tubercular foci caused by reactions and an incorrect technique is specially dangerous in the presence of mixed infections, and the treatment is thus rendered more difficult. Thus it is easily understood that those tuberculin therapists who intentionally provoke reactions see in mixed infections a contra-indication for tuberculin treatment, whereas mixed infection is no contra-indication for a *mild* tuberculin treatment.

OTHER APPLICATIONS OF TUBERCULIN. TREATMENT OF LOCAL SURGICAL TUBERCULOSIS BY INTRAFOCAL INJECTIONS.

In this section I should like to mention that realizing the dangers of sharp focal reactions, ten years ago I tried to discover a method of keeping the tuberculin away from the foci and only producing general healing actions, avoiding focal reactions which are specially dangerous in the lungs. I tried also to produce innocuous local inflammation by means of the tuberculin left at the site of injection, working on the supposition that the production of antibodies might be partly connected with inflammatory tissue-lesions due to the tuberculin. Various methods were used to attain the desired results.

Various
Attempts
to increase
Local Action.

(1) Tiny tablets of Koch's tuberculin, each of 1 mg. content, were prepared by the addition of very small quantities of milk-sugar. One such tablet was fixed every day by means of plaster (just as peas were once laid on the fontanelles) to the raw surface of a blister on the skin of the abdomen.

(2) Another method was to produce artificial œdema in an extremity by means of an elastic ligature and then make the injection, thus retaining the tuberculin at the site of injection.

(3) In other cases, I injected a mixture of tuberculin and a watery suspension of finely powdered sterile animal charcoal such as is used to decolorize animal fluids. I thought that by this means the charcoal, remaining at the place of injection, would absorb and retain a large amount of the tuberculin injected.

(4) A last method was the injection of small quantities of oil of turpentine, just as in the old practice of producing an *abcès de fixation*. The quantity used was too small to produce an abscess but simply caused local inflammation. The tuberculin was then injected into the infiltrated tissue.

The object of all these methods was this—to reduce the general action of the tuberculin and to produce local

Their Object. inflammatory action in the healthy skin at the place of injection, similar to the focal reactions of ordinary tuberculin treatment or the intrafocal tuberculin injections into a tubercular focus to be mentioned shortly. The methods were all finally abandoned, being too troublesome for the patient; I cannot, therefore, give any definite opinion of their value. The charcoal method did not seem to prevent general reactions any better than the ordinary technique, so it is very doubtful whether the charcoal really absorbed

and retained the tuberculin. A further reason for discontinuing them was that my present view of the nature of tuberculin healing, described in detail in the Theoretical Part, points to the inadvisability of keeping the tuberculin away from the tubercular foci.

Recently, my earlier standpoint has again been taken up and local skin reactions, von Pirquet's cutaneous reaction, the intracutaneous reaction (injection of minimal quantities of tuberculin into the skin itself) and Moro's percutaneous reaction (rubbing in of tuberculin ointment) have all been made use of in treatment.³⁸ I have not yet read the results of these methods.

Lastly, a few words on the local employment of tuberculin by injections into the tubercular foci, a method applicable to surgical tuberculosis, especially of the bones and joints. The object of this is quite different from that of the ordinary method of treatment, and it was founded on suggestions made by Beraneck and the experiences of Professor Roux of Lausanne and Dr. de Coulon of Neuchâtel. The method is based on the assumption, with which I agree, that in addition to the general action of tuberculin there is also a certain local action on the tubercular foci. Both lysin and antitoxin probably originate partly in the foci themselves and even the inflammatory focal reactions, resulting from the local actions of the lysinized tuberculin, have doubtless a useful side if one has the guarantee that the tissue damage caused by them is not too extensive. With this conviction, it seemed justifiable, in localized surgical tuberculosis accessible to local treatment, to combine such a local action, potent but controllable, with the general action, by injecting the tuberculin direct into the foci. Surprising success has been obtained by this

**Intrafocal
Tuberculin
Treatment.**

method in many cases of surgical tuberculosis. The original technique recommended by Beraneck consisted of the injection into the foci of relatively large doses such as 5 to 10 c.c. of the weaker solutions of tuberculin Beraneck, repeating these every week or fortnight. To exclude the danger of an excessive local and general reaction, the method has now been made milder, and much smaller doses ($\frac{1}{4}$ c.c. of the weakest solutions) are now employed; the injections are given more frequently, perhaps every two or three days, as in ordinary treatment. If the reactive phenomena which are *aimed at* are weak or absent, the concentration of the solution and size of dose may be raised as in general treatment. The object is, then, to produce, in addition to general action, local reactions to the tuberculin lysinized at the actual place of injection.

Original and Improved Techniques.

Object Justified.

This seems far more justifiable than in general treatment, as the exudation current accompanying the inflammation, directed from the blood to the morbid tissues, causes a slower and more incomplete absorption of the tuberculin than from the healthy skin. On this account, fresh activity of latent foci and general overloading with toxin are less likely to occur than in general treatment, especially as it can be assumed that part of the toxin is already neutralized by antitoxins in the foci. Thus it is possible to utilize focal reactions to advantage by relatively safe means. The value of this method seems twofold.

(1) It produces a local inflammatory action of the lysinized tuberculin. Its advantage over other means of producing inflammation once used in local tuberculosis (chloride of zinc, hetol, &c.), is that it is really specific, the tuberculin stimulating just those specific components

Results of the Method.

of the inflammatory anti-action which are necessary for the cure of tuberculosis. It is very probable that the formation of lytic and antitoxic antibodies, necessary to explain tuberculin action, takes place in large quantities at the place of injection by this method as a result of local reactions. These protective substances, acting locally in high concentration, are specially potent.

(2) As a result of his experiments (p. 123), Beraneck also assumes that by this local application of his tuberculin there occurs a direct diminution of the virulence of the bacilli³⁹ which he ascribes partly to the ortho-phosphoric acid content of the tuberculin and partly to a specific effect of the tuberculin itself on the tubercle-bacilli.

Both from the reports of patients and from personal experience, I can testify to the striking efficacy of the method in the treatment of local tuberculosis. I have used it in several cases of lupus and other forms of tuberculosis of the skin, in tuberculosis of the tarsus and ribs and in spondylitic abscesses, and am convinced of the value and safety of the method in its present milder form. It might also be tried in larger glandular tumours; this has not yet been done, however, and since swollen glands are commonly multiple, ordinary tuberculin treatment would perhaps be more rational and less dangerous.

Indications.

CONCLUSIONS CONCERNING THE PRACTICE OF TUBERCULIN TREATMENT.

I have intentionally refrained from illustrating the views and experiences that have been quoted, although a rich library of illustrations and statistics of tuberculin treatment has been collected in my clinic during the last ten years.

**Case Reports
of little
Value.**

Apart from the fact that I abominate the overloading of our literature with illustrative case reports,

such reports seem to possess but little power of argument or conviction for one who has not himself followed up the cases and observed their heterogeneous nature, especially in internal medicine. Only in a formal sense can any definite objective value be attached to the recital of case sheets and I doubt their practical use. If not a mere unarranged and bald statement, every such collection of illustrative cases is coloured subconsciously and this is specially true of a therapeutic collection; illustrations and statistics of tuberculosis from sanatorium doctors and tuberculin therapists afford unrivalled examples of this. It seems hardly possible to convince a critical reader by therapeutic illustrations. Their unreliability is largely due to the fact that no disease is so protean in its nature, or presents so many great difficulties of classification as tuberculosis. Any classification of

Classification.

cases of tuberculosis, if it is to be of any statistical value, must be made on the basis of the virulence of the infection and the sensitiveness of the patient, or rather of the relation between these two, to which I have given the name "relative virulence"; we have, at present, no exact scale for such a classification. The ordinary classification of tuberculosis into stages of disease, made in sanatoria and by tuberculin statisticians with more or less care, according to the extent and localization of the disease, body temperature, &c., has very little practical value. It should serve some useful purpose to emphasize this. It is, indeed, a great pity that in questions of treatment only personal experience and observations carry any real conviction. This is the real sense of *ars longa, vita brevis* in medicine. For this reason, and because of the limited space at my disposal, I have not burdened the reader with illustrative cases, but have only given the

quintessence of my personal experience and the reflection of this experience in my convictions. The object of this book is to give the practitioner a correct standpoint from which to consider the important question of tuberculin treatment, proceeding from which he can make personal trial of tuberculin, and use it for the benefit of his patients *without any risk*. Only his own personal experiences will supply him with the conviction of its value, and if the results are not satisfactory he must ask himself whether he has not been carrying out the treatment incorrectly, a thing more possible in tuberculin treatment than in any other therapy.

What reply shall the practitioner give to a patient who asks what prospects tuberculin treatment holds out for him? We will presume that the state

The Patient's Question.

of the disease is not such as in itself to preclude the possibility of a successful tuberculin cure. The answer will, of course, partly depend on whether he himself would eventually carry out the treatment or whether he is merely consulted as to the advisability of the patient being treated by some other practitioner. (1) Under the former condition, if the case seems suitable for a trial

The Answer.

of tuberculin, I generally say to the patient who comes to me for treatment—"I can promise you that no harm shall result from the tuberculin but I cannot guarantee to benefit or cure you; nothing but a personal trial of tuberculin will show whether your case is suitable or not. If it should happen that your case is unsuitable for tuberculin treatment, no harm will be done and we must simply try another form of treatment. Presuming that all goes well, in order to use the tuberculin treatment to the best advantage, you should, if possible, arrange for a long course of treatment, which will

demand patience. If you cannot do this, you may possibly be one of the fortunate ones who derive benefit from even a short tuberculin cure. I promise that you shall not experience any really unpleasant results from the treatment." (2) The answer is more difficult if one has to decide whether the patient should be treated by some other doctor. If the latter is known to be qualified to carry out a correct tuberculin cure the answer will, of course, be much the same. On the other hand, if he is not known or if one has an unfavourable impression of him and does not know whether he understands and approves of the technique, one cannot conscientiously say more than—"We have in tuberculin a remedy valuable in itself, but its action essentially depends upon the way in which it is used and the extent to which it is tolerated." Thus the patient will be shown that he plays a personal part in the treatment. He must be made to understand that no reactions must take place, the nature of which should be explained to him, and if such reactions do occur the dose must be reduced at once. He must therefore describe any such phenomena to his doctor so that the latter can act accordingly. In short, the general principles of the treatment are explained to the patient. Thus a certain amount of influence can be exerted on the treatment without offending the patient's private physician. To say more than this to such a patient or even to advise tuberculin treatment at the hands of a doctor one does not know, who may not have studied the question or wish to study it, is quite impossible. I think I have shown that the result of the tuberculin cure depends at least as much on the quality of the doctor as on the quality of the tuberculin; therefore it is impossible to make oneself responsible for a cure, the technique of which is quite outside one's control,

and which is so often carried out in an irrational and unintelligent manner, likely to harm the patient. Such questions will become more and more frequent in the near future, and this is the position towards them which must be taken up by a practitioner convinced of the value and rational basis of tuberculin treatment.

In speaking of the attitude of the practitioner to tuberculin treatment, I cannot forbear from expressing

Tuberculin Treatment only at the special Desire of the Patient! my astonishment that there are doctors who, as they say, "only undertake tuberculin treatment at the special desire of the patient!" It is clear enough from what

has been said that I am absolutely opposed to a doctor forcing tuberculin upon a patient against his wish; but that a doctor should allow himself to treat a patient by a method of the utility of which he is not only not convinced but of which he disapproves, at any rate to some extent, seems to be a *sacrificium intellectus* that is hardly allowable. It seems clear that in this case, as in many another, one is in duty bound to declare one's opinions openly. The whole thing is quite clear; there are only

The Three Possibilities. three possibilities — the practitioner has either studied tuberculin treatment and been convinced of its value, in which case it will be used in suitable cases; or he considers it valueless or even dangerous, which decision should be declared and tuberculin rejected; or lastly he knows nothing about tuberculin treatment, not having studied nor wishing to study it, in which case, also, he will reject tuberculin. Every doctor has an indisputable right to such a rejection but it is to be hoped that with increasing knowledge such a rejection in suitable cases will become increasingly rare. At any rate, the attitude described by "tuberculin treatment only by

express wish of the patient," placing the entire responsibility on the patient and at the same time clearly discrediting the method of treatment, is hard to justify.

It will be realized that the way of tuberculin treatment is generally somewhat difficult and long and will demand all the patience and determination of both doctor and patient. Tuberculin treatment is only possible for a section of cases and it has frequently to be abandoned. Blind enthusiasm for tuberculin treatment can hardly be laid to my charge, but I honestly believe that it is the best weapon of modern times in the fight against tuberculosis. There seems very little hope of any future

Serum Treatment of Tuberculosis. serum treatment of tuberculosis. Apart from the fact that all previous experiments in this direction have provided no positive

Its one possible Utility. and indisputable results, it seems that the possibility of an active serum treatment is for other reasons far distant. The one possible utility of serum therapy might be to rescue a patient from an acute febrile relapse, a feat which is, unfortunately, but seldom performed by tuberculin treatment. This would, indeed,

be of extreme value in face of the failure of our present methods but it seems an almost forlorn hope in really bad cases. Tuberculosis always tends to run a remittent course and so we must assume that these so-called "acute" aggravations, for which we have at present no remedy, depend on an only too chronic disorder of the healing forces of the organism; even though they begin as acute phenomena, they are predestined to become chronic and incurable and then serum treatment will be of no avail. It cannot be imagined that chronic tuberculosis could be definitely cured by a mere serum treatment, evading the thorny path of an active immu-

nizing therapy. Owing to the chronic character of the tuberculous infection, a continuous action of the protective bodies of the serum would be necessary. Experimental therapy has always failed to produce this owing to the fact that every serum, if frequently injected, displays highly toxic actions, which have been satisfactorily explained by von Pirquet's theory of serum allergia or by Wolff-Eisner's theory of albuminolysis. It is only an antitoxic serum, not a bacteriolytic one, which could have advantages

**Impossibility
of a
Continuous
Action.**

over tuberculin treatment and the antitoxic actions of the present antitubercular sera are still problematic. Although we are bound to assume that antitoxic substances are in play in the natural cure of tuberculosis and in the favourable action of tuberculin, yet it seems impossible to heap up such antitoxins in the serum of animals in sufficient quantity for therapeutic use. Up to now, this has only been done successfully in diseases caused by exotoxins, that is toxic substances secreted by the bacteria, and tuberculosis does not come under this heading; the presence of exotoxins in tuberculosis is, to say the least, very questionable. The toxins which play the

decisive part in tuberculosis are probably (as will be shown in the Theoretical Part) exclusively derivatives of endotoxins, that is of the constituents of the bacillary bodies.

Endotoxins.

Up to the present time, no antitoxins to these endotoxins have been discovered in any large quantity in the serum of immune animals. This may be either because the animal organism does not produce them in such abundance as the antitoxins of exotoxic diseases such as diphtheria and tetanus, but rather only for its own personal use, or else because these antitoxic substances

are chiefly formed in the tissues and do not reach the blood in any considerable quantity. Tuberculosis both in man and beast is, at least in its early curable stage, essentially a local disease to which the organism has become so adapted by phylogenetic development that, as the anatomical researches of Nägeli and Burckhardt show, it is generally able to overcome it by purely local processes. It seems, therefore, very probable that the antitoxic antibodies are formed locally in the tissues and do not penetrate in any great quantity to the serum, where they would be out of place for the healing of local tubercular foci. Considering the question from the

One reason
for bad
Prognosis of
Acute Cases.

general biological and phylogenetic standpoint we realize that in cases whose prognosis is unfavourable, the existence of a serum-antitoxin, which we long for, would be to the interest of the species. This circumstance, however, could not change the method of phylogenetic adaptation, directed to local defence, since these severe cases, which would otherwise not have become so bad, are destined to destruction by reason of their inborn inferiority; thus they do not reach propagation and so play no part in phylogenetic adaptation. This is the deeper reason for the very unfavourable prognosis of acute tuberculosis and the cause of the paradox that, in spite of this fact, in the great majority of cases, the organism seems to have no trouble whatever in obtaining the mastery over the tuberculous infection (Nägeli and Burckhardt, *loc. cit.*). The prospects of antitubercular serum therapy seem then to be very gloomy, since tuberculosis is, for the reasons mentioned, a disease which is notoriously unsuited for serum therapy. Setting aside the still remote possibility of reaching tuberculosis by purely chemical means, we are forced to the conclusion that

Koch followed a sound intuition when he saw in the active immunizing method of tuberculin treatment, at the time, the only successful specific treatment of tuberculosis. His original technique has, however, proved clinically impracticable and tuberculin treatment of to-day is quite a different matter.

II. THEORETICAL PART.

THE NATURE AND ACTION OF TUBERCULIN, OF IMMUNITY TO TUBERCULOSIS AND CURE OF TUBERCULAR INFECTION.

THE action of tuberculin and its special peculiarities are, indeed, striking. It has almost no effect on the non-tubercular, even on the guinea-pig, so sensitive to tuberculosis, when uninfected by tuberculosis; while in the tubercular, the smallest doses produce fever and selective organ reactions extending to the most obscure tubercular foci, and the most minute quantity is enough to kill a tubercular guinea-pig. Employed in a certain way and with a certain dosage it promotes cure of the disease. All these seemingly diverse properties of tuberculin have been, since its discovery by Koch, one of the greatest riddles of biology. Only in quite recent times has the obscurity been more and more illumined, partly by experimental observations, partly by clinical deductions. We are, therefore, to-day in a position to give a consistent explanation of these phenomena and thus to establish tuberculin treatment on a more satisfactory theoretical basis than was previously possible. The list of those who have helped to solve these difficult problems is a long one. The name of Wolff-Eisner stands high in the list and the deductions he draws from his experiments are particularly enlightening. I agree on the whole with his

**Properties
of Tuberculin.**

Wolff-Eisner.

conception of the action of tuberculin, with some modifications concerning the explanation of hypersensitiveness and the question of the existence of antitoxic actions against tuberculin. These two points of difference, however, seem essential from a clinical point of view. The theory of tuberculin action is so complicated that to make the matter clear and intelligible, I have divided it into separate sections. One of the fundamental questions is :—

THE CHEMICAL NATURE OF TUBERCULIN AND THE DIFFERENCES BETWEEN THE VARIOUS TUBERCULINS. TUBERCULIN BERANECK.

The idea is very prevalent that, under the common name of tuberculin, many preparations have been made, having essential chemical differences; this explains the continual attempt to improve tuberculin treatment by making fresh tuberculins. It is taken for granted that one special tuberculin is the tuberculin *par excellence*, the one and only, which cannot fail to cure, and that the many failures of tuberculin treatment depend chiefly or entirely on the incorrect chemical composition of former tuberculins. Tuberculins have been prepared from human and also from bovine tubercle-bacilli. In the first edition of this book, I have already declared my conviction that the conception of essential differences between various tuberculins is ungrounded and that the endeavour materially to improve tuberculin treatment by the continual preparation of new tuberculins, is futile. Good results can be obtained with all the tuberculins at our disposal if the right technique be employed. Although differences between the tuberculins with regard to their

**Various
Tuberculins.**

practical utility* undoubtedly exist, advances in tuberculin treatment are not primarily to be made by the manufacture of new preparations but in a rational use of those we already possess, and in the proper selection of cases. There can be no doubt that the

Active Principle of all Tuberculins the same.

active therapeutic principle is the same in all tuberculins. The logical conclusion is, therefore, that all tuberculins contain, to a certain extent, the same active chemical substance, the true tuberculin. Therefore it must be realized that good results can be obtained with any tuberculin if the correct technique be employed, a fact which is borne out in experience. This view is held but by few writers, of whom the chief are Wolff-Eisner⁴⁰ and Meissen.⁴¹ On the

Other Views.

other hand many authors are of the opinion that the true tubercle-toxin has not yet been found. They arrive at this conclusion from the fact that the results of tuberculin treatment still leave much to be wished, and that up to now it has not been possible to immunize animals completely against tuberculosis with the various tuberculins; we shall see, however, that other reasons account for this. A third section of authors see essential differences in the various tuberculins, believing them to consist of varying mixtures of different tubercle-toxins; therefore, following the example of Nathan the Wise in the tale of the "Three Rings," they faithfully make trial of every new tuberculin in a purely empirical manner to find out which is the best preparation for treatment. Honest though the attempt may be, it can lead to no result owing to the great differences between cases of tuberculosis, unless, based on a definite knowledge of the nature of tuberculin

* Cf. pp. 43 and 117-123, the peculiarities of Beraneck's tuberculin.

treatment, these experiments be performed with a uniform and rational technique (*cf.* note to p. 44). The latter is impossible without a knowledge of the active principle of the tuberculins. Without a theory of tuberculin treatment, one works entirely in the dark.

The common nature of this active substance in all the various tuberculins is shown not merely by therapeutic experience but by the exactly similar character of the so-called tuberculin reactions which can be produced by all tuberculins without exception. Since we cannot think of the active principle of tuberculin as a purely chemical substance, we are compelled to use physiological experiments to find out whether this active principle is identical or different in the various tuberculins. These show, in no uncertain manner, that all tuberculin reactions are qualitatively identical and only vary in degree, and thus that the active chemical principle in all tuberculins is the same.

Another conclusion can be drawn from this fact, relating to the nature of this chemical substance. The characteristic tuberculin reaction is also produced by the latest Koch's tuberculin, the so-called bacillary emulsion, which contains scarcely anything else than the most finely-powdered body-substance of tubercle-bacilli; it necessarily follows, therefore, that the active substance in this and all other tuberculins is nothing more than the protein of tubercle-bacilli or bacillary endotoxin. Wolff-Eisner comes to essentially the same conclusion; he has discovered that Ruete-Enoch's tuberculin, which only differs from Koch's tuberculin by not having been filtered through porcelain and by containing bacillary fragments, if filtered through a Berkefeld candle to remove the

**Proofs of the
Existence of a
Single Active
Substance.**

**Tuberculin a
Bacillary
Endotoxin.**

fragments of bacilli, produces reactions precisely similar to those before filtration but in a lesser degree. The fact that such preparations as Koch's old tuberculin and Denys' broth culture are filtered through porcelain and therefore do not even contain microscopic particles, by no means disproves the presence of bacillary protein as an active constituent; for the molecule of tuberculo-protein can, to a certain extent, go into solution by autolytic processes without being much changed; and even the actual bacillary protein, when freed from its external lipid coat by mechanical or chemical means, is itself partially soluble. In Beraneck's tuberculin, the protein of the tubercle-bacilli is dissolved out by orthophosphoric acid in the form of an acid albumin.

All these various preparations under the name tuberculin produce then in varying degree the same general and local reactions as Koch's bacillary emulsion which consists essentially of the body-substance of tubercle-bacilli.

All Tuberculins have the same Characteristics.

They all have the characteristic peculiarity of only producing reactions in the tuberculous organism, moderate doses being given. The similarity of all tuberculin actions to those of Koch's bacillary emulsion is a clear proof of the bacillary protein-content of all tuberculins.

A further proof is found in the experience that with all tuberculins, using the von Pirquet's cutaneous reaction, tuberculous tissue with Langhans' giant cells can be produced.^{42 43} Siegrist⁴⁴ too has been able to show that in the conjunctival reaction anatomical tubercle can be produced. At one time the tuberculins used for these experiments were not always true solutions and could not be guaranteed free from fragments of

Bacillary Fragments.

tubercle-bacilli. It had been known for some time that dead and even ground-up tubercle-bacilli can produce miliary tubercles, and therefore Pick and Daels thought at first that these anatomical changes could be ascribed

Jadassohn's Suggestion of Ultra-microscopic Particles. to the presence of such fragments of bacilli in the tuberculin. In many cases the presence of these fragments could not be proved and Jadassohn put forward the

reasonable supposition that ultramicroscopic fragments of bacilli might possibly be responsible for the tubercular nature of the local reactions. However, it was clearly proved by Zieler ⁴⁶ that these local tubercular processes could be produced not only by tuberculins in which no microscopic fragments of bacilli were to be found, but also in dialysed tuberculin, in which there could, according to current ideas, only be dissolved substances. No further proof is needed that all tuberculin solutions contain the true tubercle-toxin in the form of bacillary protein. It seems, at first sight, difficult to understand how such true solutions, which must be soon carried away from the site of injection by the lymph- and blood-streams into general circulation, can produce the same tubercular phenomena as living tubercle virus acting at the spot. The explanation seems simple if starting from the conception of Jadassohn of ultramicroscopic particles, we state that even in pure tuberculin solutions and in dialysates of them, these ultramicroscopic particles are present, as the ultramicroscope reveals in all albuminous or colloidal solutions. Products, therefore, of mechanical destruction or bacillary fragments need not come into question. This view tallies rather with the

The Micellae of Hägeli.

modern doctrines of colloidal chemistry, according to which in every albumin solution there are molecular aggregates, the micellae

of Nägeli. The fact that even dialysates of tuberculin produce tubercular phenomena does not in any way militate against the assumption that ultramicroscopic particles are at work; for even true albumins with ultramicroscopic molecular aggregates can undoubtedly be dialysed, though slowly and with difficulty. The possibility of dialysis is only a question of the size of the molecule or molecular aggregate and the diameter of the pores in the membrane and present-day physiological chemistry shows that the degree of dialysis possible is not absolute but merely relative; similarly, the division between crystalloids and colloids has become indefinite since the preparation of albumin crystals. Just as for tuberculin, so even in the case of the non-bacterial albumins (*e.g.*, of the toxic albuminous bodies of foreign serum), the assumption of ultramicroscopic molecular aggregates as carriers of their action is not merely a postulate to explain localized morbid phenomena, such as serum exanthemata; for, as a matter of fact, the ultramicroscope actually does reveal in all these cases the presence of ultramicroscopic particles which, after their introduction into the body, can well remain in the tissues without being diffused into the general circulation.

There are many differences in the method of preparation and purification of the various tuberculins. For instance, Koch's tuberculin has a large content of albumoses, which experience shows to be merely an unnecessary contamination and which Beraneck has intentionally and rightly avoided; also Koch's old tuberculin is prepared by heating, while his new tuberculin and Beraneck's are kept from the action of heat; in Beraneck's preparation, the bacillary protein is extracted with orthophosphoric acid. All these minor differences,

Minor
Differences
between the
Tuberculins.

however, alter the fundamental principles but little, and tuberculin action may be described as essentially the action of tubercle-bacillary protein. It

**Use of
Bacillary
Broth.**

should not be thought that the use of pure tubercle-bacillary broth filtrate, such as Denys' tuberculin, is any proof that the tubercle-bacilli, in addition to the toxic actions of their body-substance, possess a purely exotoxic action by virtue of any metabolic excretion or secretion. It seems to me that differences between the action of tubercle-broth and bacillary protein are only of a quantitative nature, resulting from the fact that the broth naturally only contains a small amount of bacillary protein. The addition of the fluid part of the culture in the preparation of certain tuberculins, such as Beraneck's, seems then admissible but not absolutely essential. It only appeared essential before the bacillary protein nature of tuberculin was realized, which now seems quite settled. I ought,

**Beraneck's
View.**

however, to say that this is only my own personal view, supported by some other authors such as Wolff-Eisner and Meissen, but that Beraneck himself considers the culture broth added to his tuberculin a solution of exotoxins, and its action essentially different from that of the bacillary protein. There is, however, no clear proof of this, and to retain a clear conception of the action of tuberculin, it is wiser to consider that all tuberculins are essentially the same, excluding of course the non-specific admixtures so frequently present.

It is unnecessary to describe here the characteristics of the various tuberculins; details of all the more well-known and older preparations will be found in the works of Wolff-Eisner⁴⁶ and Deutsch and Feistmantel.⁴⁷ Tuberculin Beraneck is, however, unmentioned in the one, and

**Tuberculin
Beraneck.**

only incompletely and inaccurately described in the other. I will therefore describe its more important characteristics and for fuller details refer the reader to Beraneck's treatise.* Tuberculin Beraneck is essentially a mixture of tubercle-broth, filtered free from bacilli and evaporated down *in vacuo* at a low temperature, with an extract of the bodies of tubercle-bacilli made with orthophosphoric acid; this latter, therefore, contains the bacillary protein in the form of an acid orthophosphate of albumin. As a culture-medium for both components, Beraneck employs nutritive broth without any addition of peptone and albumose. Such a culture-medium is intended to keep the tuberculin as free as possible from non-specific but nevertheless toxic substances.

The following are the special reasons for choosing Beraneck's tuberculin as the best for treatment:—

(1) The chemical nature of the preparation. It has a large content of specific immunizing substances, while the use of a peptone-free culture-medium practically excludes non-specific toxins. It has but a very slight toxic action on healthy animals, non-tubercular guinea-pigs tolerating a dose of 10 c.c. of concentrated tuberculin Beraneck (Beraneck used guinea-pigs weighing 700 to 1,000 grm.). This concentrated tuberculin Beraneck is 62·5 times stronger than the strongest solution used in treatment (H). The large content of specific substances was proved by Beraneck, who showed that 1 c.c. of concentrated tuberculin Beraneck kills tubercular guinea-pigs of the above weight. This toxicity for tubercular animals is about equivalent to that of Koch's tuberculin. The

Its Chemical Composition.

Toxicity.

* Cf. ref. ¹.

glycerine content can have no effect. This is shown by the harmlessness of the preparation for the healthy animal. Moreover, tuberculin Beraneck contains but 25 per cent. of glycerine, half the amount in Koch's old tuberculin. The high specificity of Beraneck's pre-

paration is most clearly proved by the fact that tubercular, and only tubercular patients react by fever to incredibly small doses of the tuberculin, the healthy tolerating large

doses, without displaying any signs of reaction. I recently treated a phthisical patient who displayed febrile reactions to merely $\frac{1}{20}$ c.c. of solution $\frac{A}{138}$. The infinitesimal absolute content of this amount merits consideration.

This dose is equivalent to one twenty-millionth of a cubic centimetre of concentrated tuberculin Beraneck ; this quantity contains half its weight of a filtered tubercle-broth evaporated to a syrupy consistence and, in addition, one twenty-thousand-millionth of a gramme or a twenty-millionth of a milligramme of dry orthophosphoric bacterial extract. The fact that such an infinitesimal dose can cause fever in the tubercular proves, at any rate as far as febrile reactions are concerned, the high toxicity of the preparation for the tubercular, and only for the tubercular, a specific toxicity far greater than that of Koch's old tuberculin, and one which is only paralleled by tetanus-toxin. The enormous difference between its toxicity for sound men and animals and, as far as febrile reactions are concerned, for the tubercular, is an irrefutable proof of its high and valuable specificity for therapeutic use. One important point with regard to treatment

is that while tuberculin Beraneck has a more potent action than Koch's tuberculin in causing febrile reactions in the phthisical, it is not so dangerous to life as the latter.

Freedom from Danger.

Figures show that for Beraneck's tuberculin the difference in size between the reactive dose and the fatal dose is far greater than in Koch's old tuberculin. In other words, tuberculin Beraneck has a far greater power of producing specific reactions in the tubercular than Koch's tuberculin, but such reactive doses, in the true toxicological sense of danger to life, are far less toxic than corresponding doses of Koch's tuberculin. This clearly depends on the freedom of Beraneck's preparation from unspecific toxic substances of no immunizing value.

Freedom from Contamination. Such a tuberculin is obviously just what is wanted for treatment, since immunizing processes do not depend on endangering life but on the power of the antigen to cause reactions. The purpose of tuberculin treatment is to incite an immunizing healing action and we have seen that, whether this is lytic or antitoxic, the therapeutic processes are of a reactive nature even though the so-called clinical tuberculin reactions are avoided. These considerations show that, since the reactive dose and the really harmful dose of tuberculin Beraneck lie so far apart, it is easier to produce an immunizing influence without more harm than is caused by any active immunizing action with this preparation than with Koch's old tuberculin, and possibly others. With respect to its chemical nature, then, tuberculin Beraneck is eminently suitable for therapy.

In face of these facts, the pseudo-mathematical calculations of Landmann, discrediting tuberculin Beraneck in favour of his own tuberculin, the so-called tuberculol, lose all value.⁴⁸ The testing of tuberculins by injection into healthy animals and estimation of their toxicity and therapeutic dose from the lethal dose for a healthy guinea-pig, has little practical value, as no test is made by this method

**Landmann's
Tuberculol.**

of the specific toxicity of the tuberculin. Further, the high toxicity of Landmann's tuberculol for the healthy animal, in which respect it stands unrivalled, rather disproves its suitability for human treatment; for, since its toxicity is also evident in the healthy animal, it need have no special immunizing value. On this false conception of the value of a high toxicity Landmann bases his unfavourable opinion of tuberculin Beraneck and his over-estimation of the worth of his own tuberculol. This question is discussed at length on p. 67. It is interesting to note that Landmann asserts that since his tuberculol is 5,000 times more toxic than tuberculin Beraneck, it is 5,000 times more valuable. He overlooks the natural sequence of this argument that if it were true, all cases of tuberculosis in which his preparation has been used would have been finally and definitely cured.

The ridiculous assertion has lately been made that the action of tuberculin Beraneck depends entirely on its content of orthophosphoric acid. Since even the wildest statement finds credence amongst the uninformed, this assertion must be examined, superfluous as it may seem.

We have seen that tuberculin Beraneck is composed (a) of tubercle-broth, filtered and evaporated down *in vacuo* and (b) of an orthophosphoric acid extract of tubercle-bacilli—the two components being mixed in equal volumes. Now the bacillary extract, made with 1 per cent. orthophosphoric acid and not evaporated, contains 1 per cent. of the acid and therefore the mixed concentrated tuberculin Beraneck, $\frac{1}{2}$ per cent. of the acid; $\frac{1}{20}$ c.c. of solution $\frac{A}{178}$, a quantity which can cause febrile reactions, contains, on the above reckoning, one twenty-millionth of a cubic centimetre of concentrated tuberculin Beraneck. This concentrated tuberculin Beraneck con-

tains, as we have seen, $\frac{1}{2}$ per cent. or $\frac{1}{200}$ of orthophosphoric acid. The absolute amount of this acid, then, in $\frac{1}{20}$ c.c. of solution $\frac{A}{128}$, is a four-thousand-millionth of a gramme or a four-millionth of a milligramme. It must also be remembered that these infinitesimal amounts of acid are at once neutralized by alkaline tissue juices and perfectly indifferent sodium orthophosphate is formed. It is then this amount of sodium orthophosphate that has been described as causing febrile reactions in the tubercular. It is a well-known fact that the human and animal body contains this harmless and useful salt in quite large quantities and several grammes of it leave the body daily in the urine. Therefore it is impossible to justify the assertion that the reactive action of tuberculin Beraneck depends on this small content of phosphoric acid. Finally, such a statement is directly refuted by the absence of reactions after subcutaneous injection of tuberculin Beraneck in the non-tubercular and the complete indifference of animals to injection of even proportionately larger doses of orthophosphoric acid, shown by experiments in my clinic. In von Pirquet's cutaneous reaction, Beraneck's tuberculin produces the same results as Koch's tuberculin while an equivalent solution of orthophosphoric acid is quite indifferent.

(2) Tuberculin Beraneck is a true solution of tubercle-bacillary protein, the latter being held in solution as an acid albumin. It is therefore superior to all tuberculins not filtered through porcelain and especially to bacillary emulsions in which the high dilutions cannot be accurately prepared owing to their non-homogeneous nature, and as a result, it is often impossible to foretell the action of any particular injection and a new element of danger is introduced. For this reason, I am firmly convinced

**Tuberculin
Beraneck a
True Solution.**

that the employment of such non-homogeneous preparations is one of the many reasons for the discrediting of tuberculin treatment.

(3) Beraneck's tuberculin is supplied ready for use in suitably graduated dilutions. By this means, disastrous mistakes in dosage are avoided and a quite regular graduation both of concentration and of the absolute amount of tuberculin is guaranteed. This method of dispensation would greatly enhance the value of all other tuberculins.

**Dispensation
of Tuberculin
Beraneck.**

(4) The experiments carried out by Beraneck on animals have shown the immunizing value of this preparation.

His experiments in the immunization and cure of guinea-pigs have, it is true, not given absolutely satisfactory results, but he was able, with his tuberculin, to prolong

**Immunizing
Value.
Petruschky's
Experiments.**

their life more than either he or other authors have been able to do with other tuberculins. It should also be mentioned that Beraneck has proved that specific agglutinins, an amboceptor or sensibilatrice specific to the antigen, are produced in the serum of a horse treated with his tuberculin;⁴⁹ this quite fulfils the demands of present-day research for the activity of the antigen. It is rather doubtful whether these detailed experiments are of any great value in practical treatment; at any rate, clinical experiences are of much more importance, and also the fact, experimentally proved by Beraneck, that the serum of a horse treated with his tuberculin has the power of diminishing the toxicity of his tuberculin for tubercular animals and of decreasing the virulence of tubercle-bacilli when brought into contact with them. In this connection the statement of Beraneck is of interest that, while the immune serum decreases the toxicity of his tuberculin as regards danger to life of

tubercular animals, it increases their febrile reactivity to the tuberculin. (Lysin-content responsible for passive transmission of tuberculin sensitiveness?)

**Virulence of
Tubercle-
bacilli
diminished.** Beraneck has also made the interesting and important discovery that his tuberculin has the power of weakening the virulence of tubercle-bacilli treated with it.⁵⁰ This action probably does not entirely depend upon the presence of orthophosphoric acid, but also on a specific influence exerted on the tubercle-bacilli by their own metabolic products. This phenomenon is met with in other bacteria, and is of importance in intrafocal treatment (*cf.* p. 98).

These four points will show that although all tuberculin action is similar in principle, there are practical differences between the various tuberculins, and these are such that tuberculin Beraneck is chosen as the best for treatment.

THE NATURE OF TUBERCULIN REACTIONS—WOLFF-EISNER'S LYSIN THEORY.

With the assumption of the uniform chemical nature of the active substance of all tuberculins, and the ad-

**A Special Case
of Toxic
Action of
Bacterial
Protein.** mission that it consists of bacillary protein or tubercle endotoxin, we are in a position to obtain a more exact idea of tuberculin reactions than was previously possible. It

is clear that the latter represent a special case of the toxic actions of bacterial protein. With this knowledge, Wolff-Eisner has gone another step, and brought the toxicity of bacterial proteins, especially tubercle-bacillary protein, into line with the general law of the toxicity of

**Specificity of
Tuberculin
Action.** foreign albumin. Whilst conforming to this general rule, tuberculin action is quite a special case of it. When we look rather

more closely into its specificity, two striking facts are at once realized :—

(1) Tuberculin is relatively innocuous for the healthy man and animal. Thus Koch discovered that it took $\frac{1}{4}$ c.c. of his old tuberculin to produce signs of reaction in his own body; he states, however, that $\frac{1}{100}$ c.c. is the dose which should generally produce reactions in the healthy. A dose of even 1 to 2 grm. of Koch's old tuberculin is tolerated by healthy guinea-pigs, a dose which, considering the small size of these animals and the high concentration of the tuberculin, scarcely fits in with the idea one usually associates with a bacterial toxin. A dose of over 10 c.c. of concentrated tuberculin Beraneck is tolerated by the healthy guinea-pig, although it is true that Beraneck used uncommonly large animals of 700 to 1,000 grm. weight in his experiments. I will repeat that this concentrated tuberculin Beraneck is $62\frac{1}{2}$ times stronger than the strongest solution used for treatment (H). A substance which is tolerated in such doses by healthy animals scarcely deserves the name of "toxin."

(2) Against this low toxicity of tuberculin for the healthy organism, the second fact stands out in striking contrast, that tuberculin has an extraordinarily powerful toxic action in the tubercular organism. Thus, fractions of a milligramme of Koch's old tuberculin, or $\frac{1}{10}$ c.c. of solution $\frac{A}{256}$ of tuberculin Beraneck may cause febrile reactions in a tubercular patient. This amount only represents a twenty-millionth part of a cubic centimetre of concentrated tuberculin Beraneck! *

On one side then we have the low toxicity of tuberculin for the healthy man and even for the guinea-pig,

* Cf. p. 118.

notoriously sensitive to tuberculosis; on the other side the enormous toxicity of the selfsame substance for the tubercular organism, which reacts with fever to the smallest doses of tuberculin, and displays the well-known focal reactions in the lesions, while the tubercular guinea-pig is killed by the smallest doses. These are extraordinary facts which have long been amongst the most difficult of puzzles. We will first pass in

**Earlier
Theories of
Tuberculin
Reaction.**

review the earlier theories of the nature of these tuberculin reactions in the infected organism, reactions which stand out in striking contrast to the inertness of tuberculin in the healthy organism.

(1) The first suggestion was the following:—Tuberculin, as the true chemical tubercle-toxin, acts so much more powerfully in the infected than in the uninfected organism because the former already contains a certain amount of tuberculin, preformed in the tubercular foci. The ad-

**A Summation
Theory.**

dition of the injected tuberculin to that already circulating in the body produces the general action, while its addition to the toxins which abound in the foci causes the focal reactions. This theory, however, does not furnish a complete explanation. Wolff-Eisner⁵¹ has

Objection.

shown that reactions sometimes result from the repeated injection of very small doses of tuberculin, doses whose sum-total is not large enough to produce a tuberculin reaction. This shows that mere summation phenomena do not sufficiently explain the facts. It is also difficult to understand how in latent tuberculosis, without clinical signs and without evidence that the body is under the influence of tuberculin, a minimal dose of tuberculin can cause a reaction by means of summation. If we assume with

Koch that the healthy react to 10 mgrm. of Koch's tuberculin and the tubercular generally to 1 mgrm., it is scarcely credible that in latent tuberculosis, without clinical signs, a reaction takes place to 1 mgrm. of tuberculin just because the amount injected added to that already present in the body just reaches the active dose of 10 mgrm. There would have to be exactly 9 mgrm. of tuberculin in the body of the patient; if this were so, what is to prevent small fluctuations in this amount and occasional increase to 10 mgrm. with spontaneous fever? We know, however, that this fever by no means always occurs in these cases. Further, it is scarcely logical to assume that so many cases of latent tuberculosis contain exactly 9 mgrm. of tuberculin, and always remain on the borderline of activity. Some patients might well contain merely 1 mgrm., or, in febrile cases, perhaps 20. In the former, where there is but 1 mgrm., not even a dose of several milligrammes would bring the total amount up to the point of reaction. In the latter, where there is 20, the slight increase of toxin by 1 mgrm. could hardly call forth a definite reaction. These considerations show that a mere summation theory does not sufficiently explain the facts.

(2) A possible explanation of the problem would seem to be this—that the healthy organism contains large quantities of substances antitoxic to the tuberculin (on which the health of the individual might possibly depend), and it fails to react because the small amounts of injected toxin are rendered innocuous by the antitoxin. Only when the limit of say 10 mgrm. of tuberculin injected is reached, does the antitoxin prove insufficient to cope with it and a tuberculin action is observed. It would then have to be

**A Difference
Theory.**

assumed that in active disease there is no such excess of antitoxin but a surplus of toxin, generally small; consequently, very small doses of tuberculin display activity by summation. In latent tuberculosis, it might be assumed that there exists a balance between the tuberculin and antitoxin produced in the body, so that here also small doses produce reactions. This theory would also explain why severe acute cases of tuberculosis often fail to react to tuberculin, as it could be assumed that the organism is already so saturated with tuberculin that the small additional amounts cause no sharp reactions; this explanation would apply both to local and general tuberculin reactions.

This "difference theory," the antithesis of the "summation theory," appeared to me for some time the best

Its Drawbacks. solution of the problem; it teaches that the result of the tuberculin injections depends on the relative amounts of tuberculin and antitoxin in the organism. It will not, however, bear a very close examination. In the first place it offers no explanation of the incubation period of tuberculin action, and secondly, it gives no proof of the large amount of antitoxin which it assumes is always present in the healthy. The question was taken up by Pickert and Löwenstein⁵²: they made cutaneous injections into a healthy individual of a mixture of his own serum and tuberculin, with the result that reactions still occurred and they could discover no neutralizing action of the serum on the tuberculin. Their experiments showed, however, that such neutralizing antitoxic substances are present in tuberculosis running a favourable course and in patients treated by tuberculin. This clearly does not fit in with the difference theory, which demands the presence of a greater capacity for reaction

in the healthy than in favourable cases of tuberculosis, an experience which is not borne out by the above experiments.

(3) These difficulties lead one to look in some other direction for the explanation of tuberculin reactions. One might easily be tempted to assume that Innate Sensitiveness the Chief Factor? merely the innate sensitiveness of certain individuals is the chief factor: that these individuals are generally tubercular is the result of their extreme sensitiveness and the many opportunities for infection to which man is subjected. Such an inversion of cause and effect, making the tuberculin sensitiveness the reason for, not the result of the infection, is inadmissible. First, the guinea-pig, which is very susceptible to tuberculosis, is remarkably insensitive to tuberculin as long as it is not tubercular. Secondly in man, tuberculin sensitiveness follows the development of the disease and is therefore an acquired character. This is shown by the fact that tuberculin sensitiveness, of which the cutaneous reaction affords the easiest demonstration, is very slight in infants, and with increasing age it increases parallel with the frequency of tuberculosis.⁵³

(4) At one time, a good deal of interest was taken in Hertwig's theory of tuberculin reactions.⁵⁴ He considered that the primary factor was the focal reaction and that the febrile reaction depended on it. His explanation, therefore, was entirely based on focal reactions. He argued from Stahl and Pfeffer's laws of chemotaxis. These authors have shown that a '001 per cent. solution of malic acid has a positive chemotactic or attractive action on a watery suspension of the spermatozoa of male-fern. If the spermatozoa are suspended, not in water, but in

**Hertwig's
Theory.**

Chemotaxis.

a .0005 per cent. solution of malic acid, even a .01 per cent. solution of the latter has no chemotactic action, which can then only be produced by a .015 per cent. solution. If the spermatozoa are suspended in a .05 per cent. solution, it takes a 1.5 per cent. solution to produce a chemotactic action. Hertwig considered, and his theory still has many adherents, that inflammatory processes depend entirely on chemotactic actions; he argued, therefore, that the action of subcutaneous tuberculin injections in the tubercular was this—that the leucocytes become tolerant to the bacillary toxin just as spermatozoa of male-fern to malic acid and that then the high concentration of the tubercle-toxin in the foci has a positive chemotactic action on the leucocytes, an action which was previously negative.

This theory is entirely hypothetical; it is based on the assumption that toxic inflammation depends simply on the positive chemotactic action of the toxin

Inconsistencies of the Theory.

in question; the theory is, however, unsatisfactory, for reasons which cannot be fully discussed here. For one reason, it affords no explanation of inflammatory hyperæmia. Further, it would only explain local inflammatory phenomena and Hertwig's assumption that general febrile reactions always depend on the latter is not born out in clinical experience. On the contrary, febrile reactions in the tubercular may occur without any sign of inflammatory reactions in visible tubercular foci. Lastly, the theory lays down that the injected tuberculin remains for some time in the blood, long enough for the leucocytes to become tolerant of it, a supposition which is quite opposed to the researches of Wolff-Eisner.⁵⁵

(5) One of the recent theories is that of Wassermann and Bruck.⁵⁶ By means of the complement-deviation

method, now well known and much used, they have found in the serum of patients treated with tuberculin,

a substance which with the tuberculin causes absorption of complement, and to which they have given the name antituberculin.

**Wassermann
and Bruck's
Theory.
Antituberculin.**

A substance of similar action has also been found, together with tuberculin, in the tubercular foci. From their observations, these authors have drawn the following conclusions:—

Focal reactions after tuberculin injections take place when the tuberculin meets with antituberculin in the foci and fixation of complement results.

**Their
Conclusions.**

This complement-fixation causes the softening of the tissues frequent after tuberculin injections on account of the digestive action of complement. If, on the other hand, the blood contains free antituberculin, as in a patient treated with tuberculin, the tuberculin injected is neutralized, becomes inactive and has no effect on the tubercular focus. According to this conception, general reactions are the result of focal reactions, as in Hertwig's theory. Wassermann and Bruck explain the non-reactivity of the healthy by the fact that they possess no antituberculin and no tubercular foci to cause a reaction.

The choice of the term antituberculin is rather unfortunate; it conveys the idea of an antitoxic substance neutralizing the tuberculin, while in Wasser-

**Nature of
Antituberculin.**

mann and Bruck's theory, just the opposite is really the case—the antituberculin first activates the tuberculin, attracting it to the foci. According to their conception (*cf.* p. 453 of their treatise), this antituberculin is of the nature of a bacteriolytic amboceptor. The authors do not state whether it has any actual bacteriolytic action on tubercle-bacilli.

There are many objections to the Wassermann-Bruck theory of tuberculin reactions and it does not altogether tally with the facts of the case. For one thing it is quite incomprehensible how both tuberculin and antituberculin can exist simultaneously in tubercular foci without neutralizing one another under the action of complement, which is always present. It is difficult to imagine that such a combination of tuberculin and antituberculin (if the latter is present in the foci) can cause inflammatory reactions, as by the combination at any rate chemical affinities are satisfied. Wassermann and Bruck explain that the fixation of complement by means of the tuberculin and antituberculin in the foci produces "liquefaction of the tubercular tissues"; this is hard to understand, since, if complement be brought into line with Ehrlich's conception of digestive ferments, its digestive action would chiefly be directed to the combination of tuberculin and antituberculin and would not extend to the tissues themselves. Further, the theory makes the strange assertion that the combination of tuberculin and antituberculin has on one side (in the foci) a harmful action, on the other (in the blood) a kind of detoxic action. Against the latter assumption, Strauss and Weil⁵⁷ and Wolff-Eisner⁵⁸ have shown that antituberculin, in Wassermann's sense, can be present in the serum of cases with tuberculin sensitiveness and can be absent where there is no tuberculin sensitiveness.

Objections to the Theory.

Research in Complement-deviation by other Workers.

The theory has not given an entirely satisfactory explanation of tuberculin action, yet it has excited a good deal of interest and the actual results of the work of Wassermann and Bruck have provided a valuable foundation for Wolff-Eisner's lysin theory of tuberculin reactions.

Before describing the latter, it should be mentioned that since the discoveries of Wassermann and Bruck, who only found antituberculin in the blood of cases treated with tuberculin, the same phenomenon of complement-deviation and the presence of an "antituberculin" have been proved in the blood of cases which have not undergone tuberculin treatment.^{57 58 59 60} It is true that Wolff-Eisner⁶¹ believed this substance to be non-specific in many cases; this is no proof, however, that in other cases, as Wassermann and Bruck found in those treated by tuberculin, there may not be present a specific amboceptor. Cohn⁶² has recently strongly emphasized the high specificity of the complement-deviation reaction in tuberculosis.

(6) The existence in tuberculosis of an antibody of the nature of an amboceptor is the foundation of Wolff-Eisner's lytic theory of tuberculin action.

Wolff-Eisner's Lysin Theory. In his article on the Laws of Immunity,⁶³ **Albuminolysis.** he showed that "the first injection of a foreign albuminous substance produces no immunity but always causes hypersensitiveness, which is evident on the second injection of the same albuminous substance." He further proved that "there is no difference in principle but only in degree between the action of bacterial albumin and of foreign protein derived from blood or other organs," and that "an explanation for the phenomenon of hypersensitiveness on reinjection is forthcoming if the analogy be carried a little further and one assumes that just as bacteriolysins are formed after injection of bacterial protein, so albuminolysins arise after injection of foreign albuminous substances." The latter are formed from the cells of the body-tissues as products of reaction in line with the general laws of production of antibodies. Just as

bacteriolysins dissolve up bacteria, so these albuminolysins are able to dissolve and break up the ultramicroscopic molecular aggregates, setting free from the foreign albumin, by lytic action, endotoxin-like substances which exhibit an increased toxic action. According to Wolff-Eisner, this is the cause of the increased capacity of the organism for reaction to the toxin of the foreign albumin after repeated injections, the "allergia" of von Pirquet.

Wolff-Eisner applies this theory to the explanation of tuberculin action. He assumes that tuberculin itself is

Application of the Theory. a foreign albuminous substance of low toxicity; it only displays considerable toxic action (in the form of local or general tuberculin reactions) when it meets with

Toxicity of Tuberculin increased by Lysin. a specific lysin in the body and becomes lysinized, *i.e.*, the large molecule of tuberculin is split up into smaller molecules of high toxicity by a kind of digestive process. The sensitive organism differs from the non-sensitive in that the former contains the tuberculinolysin while the latter does not or, at any rate, only in very small quantities. Thus a tubercular patient already contains lysin in his body at the time of injection, as the result of the disease. Therefore he usually displays reactions to the tuberculin by lytic action, while the healthy man does not.

As far as I know, Wolff-Eisner gives no detailed explanation of focal reactions. There are apparently two possibilities:—

Focal Reactions. (1) The lysin, increased by the tuberculin injection in question, produces an immediate acute lytic action in the foci, a cause of temporary damage resulting in inflammation in the foci. Thus an increase of lysin must precede focal reactions.

(2) Against the latter explanation, it can be argued

that the period of incubation of these focal reactions is no longer than that of general reactions, which have been ascribed to the action on the tuberculin of the lysin already present; for it must be assumed that an increase of lysin by the tuberculin demands a longer time than that required for the lytic action of the already formed lysin on the tuberculin. For this reason, the following explanation seems more probable—that the injected tuberculin, after it has been lysinized and converted into a highly toxic substance, does not merely cause fever but also the irritative actions on the tubercular foci. Thus the focal and general reactions must occur simultaneously, since both depend on the action of the lysinized tuberculin.

It may seem remarkable that the general and focal reactions, which both owe their origin to the same toxic

**All Reactions
due to Tuber-
culin Action on
Lysin present
in the Body.**

action of the lysinized tuberculin, do not always both occur but that sometimes only focal and sometimes only general reactions take place, but this seems easily explained by the fact that the two situations offer different points of attack and different capacity for stimulation. Local reactions (cutaneous, conjunctival, &c.) could be described as the direct result of the lysinized tuberculin acting at the place of application. So it can be argued that in all probability all reactions, both general and local, arising from tuberculin injections in a tubercular organism, are caused by the action of the tuberculin on the lysin already present in the body, and not by an increase of lysin due to the tuberculin, which could only take place later, as a result of the reactive processes.

Wolff-Eisner attempts to confirm his hypothesis by Wassermann and Bruck's discovery of an anti-tuberculin in the foci and in many cases, especially

those treated with tuberculin, also in the serum. We have seen that this antituberculin is not of the nature of an antitoxin, but rather resembles a bacteriolytic amboceptor, and hence would be really identical with Wolff-Eisner's tuberculinolysin. The proof of the presence of this amboceptor in cases where there is a positive tuberculin reaction (especially a cutaneous reaction) is not always forthcoming. Wolff-Eisner explains this by the fact that the technique of complement-deviation is not a fine enough test for this substance; the living organism is often alone able to prove its presence by displaying sensitiveness to tuberculin.

In short, then, Wolff-Eisner's view is that what causes tuberculin reactions and local and general damage in a tubercular infection is not the tuberculin as such but, as he puts it, a secondary decomposition-product formed from the tuberculin by the action of a lytic antibody. This will be subsequently called lysinized tuberculin.

Soon after Wolff-Eisner had stated his views of the toxic actions of foreign albumin, von Pirquet also put forward his opinion that tuberculin action is due to the antibodies of tuberculin;⁶⁶ this was in connection with his theory of serum disease (hypersensitiveness to a foreign serum⁶⁴ in man and beast after repeated injections) and exactly coincided with his views on vaccinal allergia.⁶⁵ The conceptions of Wolff-Eisner and von Pirquet are, however, very different; for, while Wolff-Eisner assumes that the antibody (lysin) causes the reaction by chemically changing and decomposing the tuberculin, von Pirquet states that the toxic action is simply caused by the joint action of the foreign albumin (the tuberculin) and its

"Antituberculin" in Wolff-Eisner's Theory.

Lysinized Tuberculin.

Differences between Wolff-Eisner's and von Pirquet's Theory.

antibody, as in serum disease. Von Pirquet gives no exact description of the nature of this joint action. The raised sensitiveness to a foreign albumin after frequent injections, resulting from the action of antibodies and evident in an increased capacity for reaction, he has called *allergia*. Wolff-Eisner's explanation is clearer and more precise, since it directly applies the analogy of bacteriolysis to unformed albumin and assumes that the increased sensitiveness depends on the presence of a

**Eber's
Tuberculo-
pyrin.**

lysin which produces toxic substances from the foreign albumin. As Wolff-Eisner acknowledges, a similar theory was suggested some years previously by Eber⁶⁷ which, however, remained unnoticed. Eber, too, assumed that the tubercular organism is able to produce a toxic fever-causing substance from the non-toxic tuberculin, to which he gave the name *tuberculopyrin*.

An interesting confirmation of Wolff-Eisner's theory of albuminolysis and lytic action of tuberculin is found in the experimental research of Abderhalden.⁶⁸ He discovered that the serum of animals treated with peptone is able to decompose peptone by a kind of ferment action, and proved this by a new and ingenious method. He followed the ferment action of the serum on peptone by the varying degree of rotation of polarized light. The results were exactly what would be expected from the decomposition of peptone and the formation of amido-acids.

Although this lytic theory of tuberculin action is to a certain extent hypothetical, yet it must be admitted

**Arguments in
favour of
Lysin Theory.**

that it offers a fairly satisfactory explanation of most of the phenomena of tuberculin diagnosis and treatment, an explanation at any rate more logical than that of any other theory and leaving but little unexplained, as I will try to show. First, however, I should like to state some of the arguments in favour of the theory :—

(1) Wolff-Eisner's conception harmonizes with the idea that tuberculin is simply tubercle-bacillary protein, and so the comparison of tuberculin reactions to the phenomenon of hypersensitiveness in serum disease after many injections is quite plausible.

(2) The assumption that by lysis (*i.e.*, the decomposition of a foreign albumin, especially tuberculin), substances of higher toxicity are formed, agrees very well with the fact that in the digestion of albuminous bodies, the products of digestion are more toxic than the original albumin.

(3) Wolff-Eisner's theory gives an interpretation of the fact that healthy men and animals do not generally react to quite large doses of tuberculin even if these be repeated. He explains this by the assumption that in the healthy, no large amount of lysin has been produced, since it has met with no tubercle-bacilli.

(4) The theory explains the incubation period of tuberculin action, since lysis naturally takes a certain time. Larger amounts of lysin shorten this incubation period, smaller amounts lengthen it. In the latter case, deferred tuberculin reactions occur.*

(5) One of the special advantages of Wolff-Eisner's theory is that it offers a simultaneous explanation of both general and focal reactions, ascribing them to the same cause, even though it be assumed that they are independent of one another. The focal reactions are put down to the irritative action of the lysinized tuberculin on the foci, the general reactions to the general action of the lysinized tuberculin in the circulation.

(6) The theory shows that the acuter tuberculin

* Cf. pp. 59-60 and 178.

reactions are a sign of more or less definite damage to the organism. This is easily understood if it be realized that these are local and general toxic actions which the non-lysinized tuberculin is not able to produce.

(7) Beraneck⁶⁹ has discovered that the serum of a horse treated with tuberculin Beraneck, if injected along with the latter into a tubercular guinea-pig, diminishes the tuberculin action as regards endangering of life, but far from decreasing, even raises the thermal action of the tuberculin. This quite tallies with the theory that the serum contains tuberculinolysin, which sets free the fever-producing substances more quickly and in larger quantity than would otherwise be the case, while the antitoxic content of the serum simultaneously confines the harmful effect of the tuberculin to the production of fever. Similar experiments have been made by Yamanouchi⁷⁰ and Bauer,⁷¹ who state that under certain conditions, tuberculin sensitiveness can be transferred by a serum. This transference of tuberculin sensitiveness by serum is confirmed by the similar experiments of Nicolle, Gay and Southerd, and Otto,⁷² all of whom found that hypersensitiveness to a foreign serum can be passively transferred to normal animals in the serum of previously treated animals. Both by these experiments and by the work of Bauer, the remarkable fact comes to light that hypersensitiveness after injection of the serum in question (containing the substance causing hypersensitiveness—lysin) is not produced at once, but only occurs after a few hours or even a day. The explanation is simple, and depends on the amboceptor-like nature of the lytic antibody whose action is only produced after it has absorbed complement, which does not take place at once.

Wolff-Eisner has unfortunately not sufficiently distinguished between the physical decomposition and the chemical dissociation

**Lytic Action
a Chemical,
not Physical,
Process.**

caused by lysin; this has made it more difficult to get a clear idea of his theory, and has given rise to a good deal of opposition from various writers. For example, on p. 259 of his treatise on "Early Diagnosis and Immunity to Tuberculin," second edition, 1909, it appears as if the author considers the artificial mechanical destruction of the bacilli in the same light as their lytic elaboration by the organism. On p. 260, in a footnote which may easily be overlooked, he corrects this idea by saying that mechanical destruction of the bacilli only assists lysin action and is by no means identical with it. A few such apparent contradictions and perplexing statements have done much to prejudice the theory. The essence of the lysin theory is, of course, the chemical decomposition of tuberculin, probably combined with the dissolving and washing-out of the formed tuberculin from bacilli and bacillary fragments. In lytic action, which is the cause of tuberculin reactions, simple physical dissolution of the bacilli plays a rather subordinate part; this is natural, since tuberculin is in itself a soluble substance, which is evident from the action of those tuberculins which are true solutions (*cf.* pp. 112-113). Whether by analogy with true bacteriolysins, complement is necessary for lysin action, is not definitely stated by Wolff-Eisner. This is probably so, if with Wolff-Eisner it be assumed that lysin is identical with the amboceptor of Wassermann-Bruck, the presence of which was proved specially in patients treated by tuberculin, and which causes deviation of complement.

Wolff-Eisner has made an addition to his theory which I cannot quite follow. He assumes⁷³ that in addition to the lytic action of the amboceptor contained

**Wolff-Eisner's
Histogenous
Immunity.**

in the blood of those sensitive to tuberculin and causing tuberculin reactions, there is another factor equally important and, as he explicitly states, entirely independent. This factor is hypersensitiveness, which occurs after repeated injections of a foreign albumin. Although Wolff-Eisner makes no statement on the matter, I am forced to conclude that he considers this hypersensitiveness (independent of lysin action) to be a phenomenon similar to the hypersensitiveness not infrequent in horses which have been immunized

against tetanus, a histogenous acquired character of the tissue-cells. This hypersensitiveness, which was also observed by von Behring, is evidenced by the fact that the horses, in spite of the large amount of tetanus-antitoxin in their blood, protecting them from an exactly equivalent amount of toxin, are killed by the smallest excess of toxin over antitoxin present, an excess which von Behring calculates to be far smaller than the fatal dose for untreated animals. He considers that this state of affairs is caused by an altered reactivity of the tetanus-sensitive tissues which have clearly suffered extensive damage.

**Explained by
the Lysin
Theory.** The hypersensitiveness is therefore histogenous. There seems, however, no sufficient reason for a similar analogy in tuberculosis if Wolff-Eisner's theory be accepted.

According to my conception, hypersensitiveness to tuberculin and living tubercle-bacilli is explained on the lysin theory simply by the large lysin content of the blood of the individual in question, by means of which very large quantities of tuberculin are quickly lysinized and an extremely potent toxic action is the result. Both sensitiveness and hypersensitiveness to tuberculin, between which there is only a difference of degree, are the result of lysin action, the action of the increased amount of lytic amboceptor of Wassermann-Bruck or lysin of Wolff-Eisner. The more lysin present, the more sensitive is the individual to tuberculin. If the definition of Mach be accepted that a truly scientific theory is one which explains the facts of a case concisely, simply and without unnecessary assumptions, the most scientific theory of the essential quality of an organism infected by tuberculosis is that it is due simply to a more or less potent lytic action without any histogenous tuberculin

sensitiveness. For the present, hypersensitiveness can be explained as the result of an increase of lysin.

It must be admitted that Wolff-Eisner's lysin theory, in itself plausible enough, can only be considered

**Passive
Transference
of Tuberculin
Sensitiveness.**

definitely proved when the passive transference of tuberculin sensitiveness by the serum of tuberculin-sensitive animals has been more fully verified. Until now, we only have the above-mentioned experiments of Yamanouchi and Bauer and the observations of Beraneck* on the action of his tubercle-immune serum, which increases febrile reactions to tuberculin. The further investigation of this important question is much to be desired. Should this transference not be confirmed, the lysin theory would not, of course, be definitely disproved, as, in experiments, the action only of small quantities of serum can be tested, quantities whose lysin-content may be insufficient to transfer the hypersensitiveness; nevertheless, if experiments prove the impossibility of passive transference, hypersensitiveness might be well explained as a histogenous phenomenon similar to Behring's hyper-

**Reactions
on the
Histogenous
Theory.**

sensitiveness of horses employed in the manufacture of tetanus serum. According to this histogenous theory, the irritative actions and reactive phenomena caused by tuberculin (not by lysinized tuberculin, as in the lysin theory) would be the result of histogenous hypersensitiveness. Therefore tuberculin would have to be considered a substance which, as such, only displays its powerful toxic actions in hypersensitive tubercular individuals as a result of an acquired peculiarity. I consider, then, that the histogenous explanation of tuberculin sensitiveness

* Cf. p. 138.

as a kind of acquired hyperæsthesia to tuberculin is quite possible and open to discussion. The production of a histogenous hypersensitiveness is no more difficult to imagine than the production of lysin. Such a hypersensitiveness of the tissues to tuberculin arising from the action of the toxin is quite in accord with the general principle of the increased function due to use. And since, as we shall see, hypersensitiveness is a means of defence, it is also intelligible from a teleological standpoint. With regard to their value, it is clearly immaterial whether defensive reactions are the

result of histogenous hypersensitiveness or are caused by a lysin. If, in the future, the histogenous explanation of hypersensitiveness should be proved correct, it seems to me that Wolff-Eisner's lysin theory will be superfluous. It must be left to future experimental research to show whether hypersensitiveness to tuberculin is explained by Wolff-Eisner's humoral lysin theory or by the histogenous theory. A combination of both, as Wolff-Eisner seems to suggest by stating that hypersensitiveness is distinct and different from lytic action, appears, as long as there is no necessity for such a dual conception, to be a pleonasm and a complication that will do nothing to promote a better understanding of the facts.

It should be clearly understood that if future research should prove the histogenous nature of tuberculin sensitiveness, the whole explanation

**Tuberculin
Action on the
Histogenous
Theory.**

of tuberculin action, both diagnostic and therapeutic, can be adapted to the histogenous theory without much alteration of the arguments used in the lysin theory. One would only have to replace the term "lytic action" by "reaction

due to histogenous hypersensitiveness." The tuberculin reaction would be a reaction due to histogenous hypersensitiveness. The essential factors of tuberculin treatment would not be the increase of lysin and the secondary antitoxin production, incited by the lysinized tuberculin, but rather an increase of the histogenous defensive reactions of the organism and the antitoxin production resulting from it. The insensitiveness of severe forms of tuberculosis to tuberculin* would be easily explained on the histogenous theory by assuming that this is simply a higher degree of histogenous tuberculin action on the tissues, in which, owing to continued tissue lesions, hypersensitiveness is replaced by insensitiveness and hyperæsthesia so to speak by anæsthesia. Thus it can be shown that all the known facts of immunity with the one exception of the passive transmission of peculiarities (serum therapy and passive transmission of anaphylaxis by the serum) can without difficulty be transferred from the humoral theory to the histopathological theory.

The possibility that Wolff-Eisner's lysin theory, although it seems to explain satisfactorily all tuberculin actions in the present state of our knowledge, may perhaps have to be eventually replaced by histogenous theory of tuberculin sensitiveness, is suggested by the important discovery of Bloch that after trichophytic infections, there occurs a hypersensitiveness to cutaneous injections of trichophytin, a toxin obtained from trichophyton cultures, quite comparable to tuberculin sensitiveness and tuberculin reactions. But this hypersensitiveness has the extremely interesting peculiarity of being conveyed to normal individuals by transplantation of small pieces of the skin and since it remains in the transplanted sections for some time, must be considered histogenous. It would be well worth while to use a similar method to test the sensitiveness of human skin to the cutaneous reaction and to find out whether cutaneous tuberculin sensitiveness can be transferred to a normal individual by transplantation of skin from a patient who has undergone the von Pirquet test.

* Cf. pp. 92-93.

THEORY OF TUBERCULIN DIAGNOSIS.

Considering the question of tuberculin diagnosis in the light of the lysin theory, it must be clear that tuberculin reactions, including all the various forms of diagnostic reactions—subcutaneous, cutaneous, intracutaneous, percutaneous and conjunctival—can be employed to a certain extent for the diagnosis of tubercular infections. All these are reactions to the lysin produced by the absorption of tuberculin in tubercular infections and to the existing hypersensitiveness to tuberculin. That in so many cases tuberculin diagnosis proves unsatisfactory is quite natural, because we do not directly diagnose tuberculosis but only the lysin-content or the hypersensitiveness of the organism. It may happen, therefore, that an individual gives a positive tuberculin reaction without having any tubercular infection. That this is sometimes the case there can be no doubt. It is most clearly seen in animal experiments; using subcutaneous tuberculin injections, Vages⁷⁴ made 2·7 per cent. false diagnoses in 7,327 cases and Nocard about 1 per cent. in 124, on the ground of positive tuberculin reactions. The reason is that occasionally even the healthy organism contains sufficient tuberculinolysin to react to the tuberculin. Lysin must be present in the healthy organism but generally in extremely small quantities and it is only increased by a tubercular infection; this is proved by the consideration that if there were absolutely no lysin in the healthy body, it could not be harmed and therefore infected by tubercle-bacilli, which would be broken down as saprophytes. Indeed, by Ehrlich's theory, the formation of antibodies including lysin can only be explained by assuming that small quantities of these are normally

**Value of
Diagnostic
Tuberculin.**

**Lysin present
even in the
Healthy
Organism.**

present in the individual and that they are merely increased by the action of antigen. The presence in normal blood of antibodies, especially diphtheria-antitoxin, can be definitely proved. It can, therefore, be taken for granted that there is a potential lysin formation in the normal individual but that any large store of lysin is only exceptionally present. For this reason, the healthy body only occasionally reacts to moderate doses of tuberculin.

It is still undecided whether the febrile reactions which can be produced in the healthy by very large doses of tuberculin are due :—

- Febrile Reactions in the Healthy.**
- (a) To the large amount of less toxic non-lysinized tuberculin as such or
 - (b) To the small but sufficient quantities of lysinized tuberculin which may be formed from the larger amount of tuberculin injected.

The latter explanation seems quite possible, as in cases of tuberculosis which exhibit no general reactions to tuberculin and therefore probably only possess a small quantity of lysin, the cutaneous test often gives a positive result on account of the high concentration of the toxin used. In this connection, skin-reactions without general reactions in the tuberculin treatment of severe cases should be noticed (p. 98).

On the other hand, reactions are sometimes absent even though there is unquestionably a tubercular infection; this is seen in slight, inactive cases, where the disease has become stationary; here, the lysin-action is reduced to a minimum by the slackening down of the tuberculous process, so that the small amount of tuberculin injected does not furnish enough lysinized tuberculin to produce a reaction.

Reactions to tuberculin are often absent in really severe cases. There are three possible explanations of this :—

- Absence of Reactions in slight Cases of Tuberculosis**
- (1) The body may already contain such an excess of lysinized tuberculin, that the extra amount of tuberculin injected does not display any action or
- and in severe Cases.**

(2) The tissues may be so much damaged that they can no longer produce any lysin or

(3) Because the lysin has already been so far neutralized by the tuberculosis, that the diagnostic tuberculin finds no free lysin to act upon and therefore proves inactive (lysin-deviation).

The last explanation is borne out by Römer's⁷⁵ statement, that the occurrence of hypersensitiveness to serum can be prevented for a certain length of time by a single injection of a large quantity of serum or several injections of a moderate quantity. It seems that there can be no other explanation than this—that the antibody (according to Wolff-Eisner, an albuminolysin) causing the hypersensitiveness is completely neutralized by the large amount of serum for a certain length of time, and lack of complement or insufficient lysin-saturation of the serum bodies injected prevents lytic action. The result is that subsequent injections of a much smaller dose of serum find no free lysin and therefore produce no signs of hypersensitiveness.

The lysin theory also provides a simple explanation of the reverse fact, that diagnostic tuberculin reactions are obtained in anatomical tuberculosis when there are only stationary, inactive foci, cases considered as cured and of no clinical importance. It seems that in these individuals also there may be sufficient lysin in the body to produce a reaction. This fact is of importance in the consideration of the specificity of tuberculin reactions. One has only to realize that quite inactive foci can cause tuberculin reactions, and that such are nearly always present in adults (Nägeli and Burckhardt), to be persuaded that positive tuberculin reactions are specific in the majority of cases, and point to the presence of tuberculosis which may, however, be completely cured and inactive. Since Nägeli and Burckhardt have proved the presence of these inactive foci in nearly every adult person, such a fine method

**Reactions in
Inactive
Anatomical
Tuberculosis.**

**Specificity of
Tuberculin
Reactions.**

of diagnosis which discovers inactive or even cured tuberculosis is of limited clinical value. It is well known that von Pirquet's cutaneous test is of very little real clinical value as a means of diagnosis, as it so often proves positive in quite inactive tuberculosis when no general reactions can be produced. This is probably because the tuberculin applied locally acts on the tissues in such high concentration, that even by the smallest quantities of lysin, enough tuberculin is lysinized to produce a cutaneous reaction by means of the high local concentration. I will repeat what was said

**A Quantitative
Cutaneous
Test.**

on p. 86, that I attempt to avoid this drawback by making the test simultaneously with varying concentrations, some extremely low. If, as frequently happens, the lowest concentration, 1 : 1,000 of Koch's tuberculin, gives a positive result, I repeat the test with still weaker solutions of 1 : 10,000, 1 : 100,000 and so on. In this manner, the sensitiveness of these local reactions can be reduced at will so that the test shall give a positive result only in active tuberculosis. Wolff-Eisner states that this is the case in his conjunctival reaction, but other writers have not found this to be so. For the time being, I cannot give any definite opinion on the point. I intend to employ this quantitative cutaneous reaction to test tuberculin sensitiveness and thereby to obtain an estimate of the size of the best initial therapeutic dose of tuberculin. It will not, of course, be a very definite criterion, as the skin may quite possibly have its individual degree of sensitiveness, which may be different from that of the lungs and other internal organs. It should be mentioned that tuberculin Beraneck is specially suitable for this cutaneous test, as it has a purer specificity than Koch's tuberculin. The use of tuberculin Beraneck is specially advisable when it is also

to be used for the subsequent treatment. Although I have recommended the use of this safe and harmless method, which is not without some prospects of success, I again state that diagnostic tuberculin injections are dangerous and therefore inadmissible and they exhibit just as great difficulties of interpretation as superficial reactions.

An explanation of the facts of the tuberculin reaction on the theory of histogenous hypersensitiveness is given on pp. 142-143. This would have to be the interpretation if the lysin theory were proved incorrect.

NATURAL IMMUNITY TO TUBERCULOSIS.

RELATION OF TUBERCULIN SENSITIVENESS TO THE ÆTIOLOGY, COURSE AND PROGNOSIS OF TUBER- CULOSIS, SCROFULA AND LYMPHATISM.

IN considering tuberculin action and tuberculin sensitiveness other questions arise, especially concerning the natural course of an infection, prognosis, and immunity in tuberculosis.

It should first be noticed that all the latest research has shown that hypersensitiveness to tuberculin has the **Close Connection between Hypersensitiveness and Immunity.** very closest connection with immunity to tuberculosis. This connection between hypersensitiveness and immunity is also to be found in other infections. In von Pirquet's⁷⁶ experiments in vaccination; his conception of "allergia," closely connected with immunity, is simply a conception of hypersensitiveness. Römer⁷⁷ was certainly right in suggesting that the term "allergia," which does not clearly explain the phenomena it represents, should be replaced by hypersensitiveness. In tuberculosis, the connection between hypersensitiveness and immunity is

specially emphasized by Wolff-Eisner (*loc. cit.*), Römer, and Hamburger.⁷⁸

The most important research in immunity to tuberculosis was the fundamental discovery of Koch that if guinea-pigs which are already tubercular are again infected with tuberculosis by cutaneous inoculation, this second infection does not develop, but immediately produces ulceration which heals quickly and permanently without infecting the neighbouring lymphatic glands. Thus the first infection has produced local immunity to a second infection and, according to Koch's description of the course of the second infection, there can be no doubt that this immunity is connected with, and caused by, hypersensitiveness. This is shown by the fact that immediate inflammatory and necrotic changes take place at the site of the second infection, while after the first infection local changes only begin to develop in fourteen days. According to Wolff-Eisner's theory, by analogy with the hypersensitiveness of tuberculin to tubercular guinea-pigs, we can consider this hypersensitiveness an action of the lysin which, in these animals, is increased by the disease; this the more since we have already seen that there is no difference in principle between tuberculin and the protein of living tubercle-bacilli. Hamburger⁷⁹ has made a special study of this phenomenon in the super-infection of guinea-pigs, and has come to the conclusion that it is a sign of immunity dependent on hypersensitiveness or allergia, in which the organism immediately repels the infection by an acute reaction of its natural inflammatory healing forces (pp. 15-21). From the acuteness of the local phenomena which follow the super-infection, he concludes that the existence of hypersensitiveness to

Koch's Experiments in Super-infection. Immunity due to Hyper-sensitiveness.

Hamburger.

tuberculin probably signifies a certain degree of immunity of the individual to tuberculosis. Römer⁸⁰ has also made similar experiments on guinea-pigs which prove that a second infection does very little to extend the tubercular lesions caused by the first infection. The conditions are very similar to those in syphilis, where also a second infection does not develop if the first is still florid. Here also Finger and Landsteiner⁸¹ have proved that there is no complete insensitiveness to the second infection, but only a changed capacity for allergic reaction, analogous to the phenomenon of hypersensitiveness in tubercular guinea-pigs.

The unfavourable side of this hypersensitiveness is also of interest, and has been investigated by Bail.⁸² This author showed that if, in tubercular guinea-pigs, the super-infection consists of the intraperitoneal injection of very large numbers of tubercle-bacilli, the animal dies in a few hours, while normal animals, subjected to the same treatment, only commence to show symptoms in twenty-four hours. This experience quite tallies with the well-known fact that tubercular guinea-pigs are killed by small doses of tuberculin, doses quite innocuous to the healthy animal. The cause of the hypersensitiveness of the diseased animals is that the body-substance of the tubercle-bacilli and the tuberculin have been converted into a dangerous toxin by the action of the lysin, which has been increased by the infection. While, in the previously described experiments of Koch, hypersensitiveness acts as a means of defence, in this case it is disastrous for the animal. This is easily understood if it be assumed that the hypersensitiveness is a question of lytic action.

if only small quantities of tubercle-bacilli are used in the second infection, they are lysinized and the secondary toxin formed (lysinized tuberculin) produces acute inflammation. The second infection does not develop because of the protective action of these reactive processes and also possibly because the lysin not only lysinizes the tuberculin, but also the living tubercle-bacilli, weakening or killing them. On the other hand, if large quantities of tubercle-bacilli, or an amount of tuberculin which is just innocuous for the healthy animal be employed, the amount of lysinized toxin set free by lytic action is sufficient to kill the animal. Thus Wolff-Eisner⁸³ is quite right in saying: "Any means of defence dependent on hypersensitiveness is a two-edged weapon, which may easily be a danger to the body carrying it." This fact clearly shows the two-edgedness of therapeutic tuberculin reactions, a point which was emphasized in the Practical Part.

This question is well illustrated by the interesting observations of Römer⁸⁴ on cattle. Using von Behring's method, he vaccinated them with a particular human strain of living tubercle-bacilli, non-lethal for cattle and thereby immunized them to severe infections, fatal for control animals. If the vaccinated and non-vaccinated animals be simultaneously injected with large doses of highly virulent tubercle-bacilli, the latter usually show no signs of reaction during the first few days but subsequently die of tuberculosis after a shorter or longer incubation-period. The vaccinated animals, on the other hand, show immediate acute febrile reactions which, however, gradually subside and give place to a complete cure. Thus the so-called immunity of the vaccinated animals is

**Vaccination
of Cattle with
living
Tubercle-
bacilli.**

bound up with a capacity for increased and more rapid local reaction, *i.e.*, with hypersensitiveness. These facts entirely bear out the lysin theory of tubercle-toxin and immunity to tuberculosis.

It should be noticed that recently a very interesting analogy to the conditions in immunity to tuberculosis has been found in trichophytic infections. Bloch⁸⁵ has shown that trichophytosis in rabbits, and also probably in man, produces active immunity to trichophytosis in general, not limited to one species of trychophyton, which is accompanied by phenomena of hypersensitiveness quite analogous to those in tuberculosis. Bloch has used the filtrate from old trichophyton cultures (trichophytin) like a tuberculin and has shown that it produces cutaneous reactions in rabbits and human beings who have once recovered from trichophytosis and have become immune, just as does tuberculin in tubercular patients. Remarkably enough, this trichophytin sensitiveness seems to be a histogenous phenomenon, since Bloch has transferred it to normal individuals, at any rate for a certain length of time, by means of skin-grafting.

This remarkable fact points to the possibility that the humoral lysin theory of hypersensitiveness may perhaps have to be replaced by a histogenous theory (*cf.* p. 143). It seems to me that if Wolff-Eisner's lysin theory turns out to be correct, it will itself quite suffice to explain hypersensitiveness; Wolff-Eisner himself, however, assumes an independent, probably histogenous hypersensitiveness which seems, as I have already stated, to be quite superfluous, as either the humoral lysin theory alone or else the histogenous theory quite explain the phenomena of hypersensitiveness.

With this explanation for Römer's phenomena of immunity in cattle, it can easily be understood that other workers have not obtained such good results as Römer himself from von Behring's method; Vallée and Rossignol⁸⁶ and also Weber and Titze⁸⁷ rightly came to the conclusion that von Behring's defensive vaccination does not produce true immunity but is simply a means of relative defence. It is clear that the protective force of mere hypersensitiveness varies in different individuals.

From Römer's results and the similar experiments

**Bloch's
Immunity to
Trichophytosis.**

**Immunity in
the old sense
distinct from
Immunity
due to Hyper-
sensitiveness.**

of von Pirquet in vaccinia, it seems evident that a distinction must be made between

(a) Immunity in the old sense of the word by which it is understood that infection and intoxication are prevented by the insensitiveness of the immune individual and

(b) Immunity by hypersensitiveness.

In the interests of a clearer explanation of the conditions in immunity, I consider it advisable to substitute, in general pathology, the latter unambiguous expression for the somewhat vague term "allergia" adopted by von Pirquet.

It must be admitted that it is quite conceivable that future research will prove immunity in the old sense of the word to be in reality also an immunity by hypersensitiveness; in this case the general conception of immunity would be merged in that of hypersensitiveness.

It is, indeed, quite within the bounds of possibility that hypersensitiveness to infections may reach such a high degree that the harmful action of the infecting agent is so-to-speak nipped in the bud by the anti-action of the organism. In this case, the phenomena of hypersensitiveness (*e.g.*, such as are seen in experiments in super-infection) may not be clinically manifest. This will

be the case when the hypersensitiveness immediately stimulates the whole array of reactive protective processes to such rapid and faultless action that the toxin, in its first attempt to harm the body, is foiled without these reactive processes coming under clinical observation. It is conceivable that the first stages of the reactive process (inflammation and general toxic action) are at once annulled by the commencement of the

Non-manifestation of Hypersensitiveness.

The Cause.

secondary protective processes (antibody production) so that the net result is a seeming insensitiveness to the toxin of the disease. We shall also see shortly that the insensitiveness to tuberculin occurring in tuberculin treatment is, in respect of its therapeutic activity, in all probability to be similarly considered, *i.e.*, that it is only an apparent insensitiveness but that there is really a high degree of hypersensitiveness which, however, so acts that the inflammatory and febrile phenomena of hypersensitiveness (lytic action) are not manifest, being immediately counteracted by the anti-toxic action produced.

It seems to me that whether one considers hypersensitiveness to be explained by humoral or histogenous processes, the whole pathology of infectious diseases needs thorough revision and consideration from the standpoint of the theory of hypersensitiveness. In my clinic, I have, of late, always advocated the view that the recurrence of articular rheumatism, pneumonia and erysipelas is simply the result of acquired hypersensitiveness and that it is accompanied by protective actions which (at any rate in pneumonia or erysipelas) render the course of the relapse milder and generally also shorter than in the first infection. By virtue of a previous recovery from these diseases, the organism acquires a hypersensitiveness and therefore, when again exposed to the infecting agent, relapses more quickly and more frequently than the healthy organism. On the other hand, just because of its hypersensitiveness and the resulting production both of the non-specific inflammatory (pp. 17-20) and the specific antibodies, it recovers more quickly and more easily from the infection than the normal organism.

**Need for
Revision of
Pathology of
Infections.**

**Recurrence of
Pneumonia, &c.**

Just as in progressive tuberculin treatment, the hypersensitiveness is not clinically perceptible but is only evident as a seeming insensitiveness in this milder course of the disease. This acquired hypersensitiveness, apart from the danger of more frequent recurrence, will naturally prove an unfavourable phenomenon if it be accompanied by a deficient capacity for reaction. This is the case, for example, in chronic articular rheumatism.

This theory of the relapses in such diseases, a theory based on hypersensitiveness, is diametrically opposed to my earlier conception and the suggestions of other writers. The old explanation of these relapses was based on the supposition that the cause of the disease remains in the body,

**The Old
Explanation
of these
Relapses.**

a well known fact in osteomyelitis; therefore relapses take place more frequently but run a milder course owing to the acquirement of a certain relative immunity due to the first infection. If this were true, one would have to make the rather doubtful and difficult assumption that this relative immunity mitigates the course of the disease but does not reduce its morbidity or incidence. From this example, it is evident what a different aspect is put upon the conditions of immunity from the moment when one begins to get away from the old idea, which is a dead-weight to research, that every infectious disease must be immunized by insensitiveness in the old sense of the word, *i.e.*, by purely antitoxic or direct bacteriolytic means. The new aspect

**The New
Explanation.
Importance
of Local
Reactions.**

seems to promise much for the furtherance of our knowledge, especially as it brings us back to a more exact valuation of local tissue and cell-reactions. Von Behring's humoral-pathological theory of infectious diseases, justified as his conception may seem in particular cases, has

resulted in an underestimation of the value of these local reactions. If the correctness of this theory of hypersensitiveness be granted, a theory which emphasizes the importance of inflammation and

Limited Value of Serum-Therapy. other local reactions in the cure of an infection, it is clear at a glance that no curative sera can yet have been made for many infectious diseases, and that in all probability none will ever be made; also that the generalization of von Behring's discovery in diphtheria and tetanus was only a dream which will never come true. Indeed, if it be clearly realized that the method of cure of pneumonia, erysipelas and articular rheumatism consists essentially in local reactions and that, therefore, the organism must use its own defensive forces, it is evident that there can be no serum of prompt action and unequivocal value against these diseases. The fact that animals can be immunized against streptococcus, for example, is no argument against this histopathological or histochemical standpoint; the apparent immunity, obtained by injections of streptococci, seems, by the clinical phenomena, to be no true immunity in the old sense but just an immunity by hypersensitiveness, in which the battle is chiefly fought by the tissues. The successful results obtained by streptococcal serum, unfortunately rare and capricious, are explained by assuming that the immunity due to hypersensitiveness of the serum-giving animal has a humoral component, since an increase of lysin takes place. Therefore it is conceivable that the transference with the serum of a certain amount of hypersensitizing lysin may, under favourable conditions, have a useful action; but the direct and definite cessation of morbid symptoms which occurs in a toxic disease like diphtheria, cannot

Lysin-content of Serum.

be expected, since the law of the definite relation between action and anti-action only holds good for toxins and antitoxins. Thus the action of a hypersensitizing substance in the serum only acts as a stimulus to active immunization and in the end, the tissues themselves have to undertake the extermination of the infection. The lysin itself does not cure, as even if it destroys some bacteria, it does not destroy all; it merely stimulates the healing action by promoting reactions of hypersensitiveness. The uncertainty of the result also depends on the following fact, which constitutes a special difficulty and is sometimes overlooked. The amount of serum injected represents but a small fraction of the blood of the animal in which it has produced lysin (primarily for its own use) and, as experience shows, there remains no great excess for other purposes.

The experiments in super-infection explain a large number of important phenomena in the pathology and ætiology of tuberculosis. They explain why, at a certain stage in human tuberculosis, although the tubercle-bacilli are doubtless present in the general circulation, the disease does not often attack fresh organs; this is clearly the result of lytic immunity to super-infection by hypersensitiveness, the disseminated tubercle-bacilli being made innocuous by the lysin and the reactive processes caused by it. This has been proved in tubercular guinea-pigs by Weleminski.⁸⁸ They also explain why, in phthisical patients, in whom large numbers of tubercle-bacilli pass over the laryngeal mucous membrane or are swallowed, spreading of the infection by this means frequently does not take place. Here, too, it is clearly a case of protection against super-infection by lytic hypersensitiveness. The fact has lately been established that in the phthisical,

**Reasons for
Non-extension
of Tubercular
Disease.**

tubercle septicæmia with abundant tubercle-bacilli in the blood not infrequently occurs without giving rise to miliary tuberculosis.⁸⁹ The tubercle-bacilli are evidently either directly lysinized or are rendered innocuous by tissue-reaction at the moment when they attack the tissues.

Miliary tuberculosis must be caused either :—

(a) By such a great surcharge of the blood with tubercle-bacilli that no potent lytic actions or hypersensitiveness are available as a means of

**Cause of
Miliary
Tuberculosis.**

defence; or

(b) By the suppression of the lytic forces (mentioned in the section on tuberculin reactions) evidenced, in severe cases, by the absence of tuberculin reactions.

This suppression of the lytic forces may depend either on general damage to the organism which deprives the cells of their lysin-producing capacity, or else on the fact that the lysin is used up by the tubercle-bacilli in the tubercular foci.

The lysin theory affords a good explanation of the experience of Marmorek,⁹⁰ that in guinea-pigs infected

**Tubercle-
bacilli
weakened by
Lytic action.**

by tuberculosis, tubercle-bacilli are found in the blood thirty-five days after their injection, and that their virulence seems to be weakened; this is in all probability due

to lytic action. Lastly, it should be mentioned that Kiralyfi⁹¹ found that the tubercle-bacilli in the sputum of patients treated with tuberculin are weakened as a probable result of lytic action. In this connection I refer the reader to the experiments of Beranek and Marmorek in the action of tubercle-immune serum on living tubercle-bacilli.*

* Cf. pp. 123 and 178-179.

The theory of the protective action of hypersensitivity by lytic action also seems to explain the fact that children who have once got over a tubercular infection of the lymphatic glands seem to command a certain relative resistance to other localizations of tuberculosis, and that patients with tubercular spondylitis or other forms of osseous tuberculosis show no special predisposition to pulmonary tuberculosis. It is a singular fact that tubercular meningitis by no means often occurs in severe febrile forms of tuberculosis, but much more commonly in quite latent tuberculosis of the bronchial glands. This seems to be explained by the fact that in the latter form, which is generally inactive and clinically latent, the hypersensitiveness and lytic action are too small to cause a rapid destruction of the tubercle-bacilli in the circulation.

Relative Immunity acquired as a Result of Infection.

This conception of tuberculin action provides an explanation of the so-called cutaneous tuberculides.⁹²

Cutaneous Tuberculides.

Wolff-Eisner assumes, and I believe rightly, that this skin trouble, the nature of which is still much in dispute, but which is of importance in diagnosis, is caused by the abortive dissemination of tubercle-bacilli in those already infected by tuberculosis. The dissemination of bacilli only runs an abortive course, as these are hypersensitive individuals with relative defence against superinfection. The tissue changes are therefore not always specifically tubercular, but are rather of an inflammatory nature, and the tubercle-bacilli in the tuberculides are either increased but little or not at all, or even quickly destroyed. For this reason tubercle-bacilli are seldom found in cutaneous tuberculides.* Some authorities have

* A short time ago tubercle-bacilli were found in a papulosquamous tuberculide in a child attending my clinic.

explained tuberculides as pure toxic actions; this was first suggested by Klingemüller²² from observations on patients suffering from this affection, and more lately by histological research in the cutaneous test.* The argument is used that with tuberculin filtered through a Berkefeld filter, and therefore containing no bacillary particles, tuberculides and true tubercles can be produced; the argument is unnecessary, however, if it be assumed that the tuberculides are caused by the abortive dissemination of tubercle-bacilli and subsequent bacteriolysis. I have already suggested that certain forms of chronic arthritis are due to tuberculides of the joints (*cf.* p. 80) and that many obscure affections of internal organs may possibly be due to the same cause.

Lastly, many ætiological facts can be explained by the theory of lytic hypersensitiveness in immunity to tuberculosis. Thus, many observers have noticed that men who come from a district more or less free from tuberculosis and move into large towns very frequently contract the disease and often in a particularly acute form. Such persons who have not been exposed to tubercle-bacilli in their previous life, have never been infected by the disease in its mild curable form (seen in the anatomical researches of Nägeli and Burckhardt, *loc. cit.*), and therefore possess no hypersensitiveness or the relative protection due to this. If then, by reason of the abundance of tubercle-bacilli in large towns, they become infected, they have no power of resistance owing to their lack of hypersensitiveness. This explanation also holds for the fact that negroes, when they migrate to Europe, are very prone to

**Ætiological
Facts ex-
plained by
Lysin Theory.**

* *Cf.* pp. 118-115.

contract tuberculosis, a disease rare in their native countries. Römer⁹⁴ states, too, that the same thing happens to dwellers in the country districts of the Argentine when they emigrate to the large townships. Monkeys in zoological gardens often die of tuberculosis, which is very rare in their natural state.⁹⁵ Römer also quotes the fact that in bacteriological laboratories, where much work is done with tubercle-bacilli, which are often sprayed out into the air from platinum wires heated in a flame, the workers are seldom infected by tuberculosis; this is just because the hypersensitiveness, acquired by most people, is specially easily attained by these individuals owing to the circumstances under which they are working. This almost universal hypersensitiveness is proved by the results of von Pirquet's cutaneous test, which is nearly always positive in adults.

From these facts, Römer⁹⁶ and Wolff-Eisner, whom he quotes in this connection, justifiably conclude that since

**Necessity of
avoiding
Severe
Infections.**

the inactive tuberculosis which is almost constant in adults is probably a powerful defence against severe forms of the disease, it is less essential scrupulously to guard against all infection (which can seldom be done in practice) than to try to prevent severe infections, against which the organism is unable to protect itself by the mechanism of a rapidly developed hypersensitiveness. This and other considerations point to the importance of the isolation of severe cases.

This protective action of a tubercular infection against superinfection should be a great comfort to those phthisical patients sent to a health resort who so often fear that they may there acquire fresh infection.

We have seen, then, that the theory of the protective action of an acquired hypersensitiveness to tuberculin

itself, best interpreted by Wolff-Eisner's lysin theory, explains a whole series of interesting facts in the ætiology and pathology of tuberculosis, which were previously quite unintelligible.

The reader will, perhaps, ask the question: "If an existing tubercular disease is such a defence against super-

infection and spreading of the disease to other organs, why is it that the primary infection itself does not always heal as easily as it prevents superinfection?" In other words,

Tuberculosis generally heals spontaneously.

"Why does not tuberculosis heal as a general rule if the organism is master of such an excellent protective mechanism?" In the first place it should be noticed that in point of fact, as the statistics of Nägeli and Burckhardt show, tuberculosis does as a rule heal spontaneously. These statistics prove that nearly every adult has had a tubercular infection which is generally cured, since, as is well known, only about one-seventh of the population die of the disease. To explain the non-healing of a limited number of cases, the following considerations should be taken into account.

Severe and extensive localizations of tuberculosis are caused by the fact that for some reason or other, such as constitutional peculiarity or weakness

Reasons for Occasional Non-healing.

due to intercurrent pathological influences, the natural defensive forces of the organism are absent. These, as we have seen, chiefly consist of lytic actions. If, as a result, a large active tubercular focus is formed, it naturally offers more resistance to healing than commencing metastasis or even a fresh infection from outside, since in the large focus there is a specially large number of tubercle-bacilli against which the anti-actions of the organism (especially lytic anti-actions) are often insufficient. It must also be

remembered that the non-vascularity of the tubercles and the inclusion of the tubercle-bacilli when once settled in the cells are both obstacles in the way of favourable lytic action. It should also be considered that if it is a question not of initial disease but of extensive processes, the prospects are naturally unfavourable in cases where, although the lytic actions are sufficient, antitoxic actions are not present. In these cases the lytic actions alone may sometimes do more harm than good (as Bail has shown in his experiments) by the production of large quantities of toxins formed by lysis* (lysinized tuberculin) to which the organism is not adapted. In the section dealing

**Detoxication
by Antitoxic
Substances.**

ing with the theory of tuberculin treatment, it will be shown that the assumption that these toxic bodies are rendered innocuous in favourable cases by antitoxic substances is absolutely necessary. These antitoxic substances, as we have seen in the Practical Part, are partly specific immunizing antibodies, partly non-specific combinable material contained in the inflammatory exudation.† It is now easy to realize that in a severe and extensive tubercular focus, this detoxication may not take place. The result will be the intervention of those severe and generally incurable conditions which, in the Practical Part, we have called toxic surcharge and in which the whole organism is under the influence of lysinized but not neutralized tuberculin. There is another

**Adaptation of
Tubercle-
bacilli.**

difficulty in the way of curing the larger tubercular foci:—both by the Darwinian theory of selection in the struggle for existence and the Lamarckian principle of direct adaptation,

* Cf. p. 150.

† Cf. pp. 15-20.

pathogenic micro-organisms in general, certainly including tubercle-bacilli, when once settled in the tissues, become adapted to their new surroundings. Thus the anti-actions of the organism, able to counteract a commencing infection, become increasingly powerless and the invading micro-organisms get the upper hand. The tubercle-bacilli disseminated in the blood-stream or even entering the system from outside can, however, easily be rendered innocuous by the lytic actions of the organism,

as they have not become adapted to their new mode of life. This fact—that great

Weibel.

numbers of tubercle-bacilli massed in the larger tubercular foci offer greater resistance

to natural healing than bacilli emanating from the foci into the circulation—finds an analogy in the researches of R. Weibel.⁹⁷ He discovered that one and the same quantity of virulent staphylococci is much less harmful and produces less suppuration when injected into several different situations than when injected all at once into the same spot.

All this present-day research into immunity to tuberculosis has also thrown light on the difference in nature

Difference between Localized Pulmonary Tuberculosis and General Miliary Tuberculosis.	between localized pulmonary tuberculosis or other forms of the disease occurring in large foci and general miliary tuberculosis. Römer, in his experiments in super-infection of tubercular guinea-pigs, made the following observation. If the second infection, either with respect to the number of bacilli or their virulence, is so severe that it is not completely counteracted by the reactions due to hypersensitiveness, pulmonary tuberculosis with cavities is developed in nearly every case, and this hardly ever occurs in the first infected animals. Römer therefore concludes that ordinary adult tuber-
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culosis is the result of the massive superinfection of an individual partially immunized (by the mechanism of hypersensitiveness) by a previous tubercular infection in his youth.

He leaves undecided the origin of the superinfection and considers it possible that, in some cases, there arise auto-infections from already existing localizations of the disease, the cause of which needs further investigation: in others, it may be a case of massive superinfection from outside. This conception confirms the view mentioned on p. 161, with which Wolff-Eisner and Römer agree, that the avoidance of severe infections should be one's chief aim.

The new doctrines of hypersensitiveness also seem to give a clue to the nature of scrofula. That the nature and symptoms of scrofula are not sufficiently described by its definition as glandular tuberculosis is evident from the time-worn designation of scrofula as an inflammatory diathesis. Until now it has not been possible to get any clear idea of this inflammatory diathesis, or exactly to define the definite connection of this constitutional anomaly with glandular tuberculosis. A clearer conception of the facts of the case has been prepared by the theory put forward by Moro and Doganoff,⁹⁸ Escherich,⁹⁹ Bauer and Engel.¹⁰⁰ These writers suggest that scrofula is to be considered as hypersensitiveness to tuberculin, acquired by the influence of a tubercular infection, generally of the lymphatic glands; on this hypersensitiveness depend the well-known eczematous and inflammatory phenomena of the skin which characterize scrofula. These authors have also proved that in these patients the scrofulous changes in the skin run a course exactly parallel with the tuberculin

sensitiveness as shown by the cutaneous test. Escherich (*loc. cit.*) has drawn graphic illustrations of this parallelism, which are especially instructive and convincing. It is true that the question of how these scrofulous skin-changes are to be explained by tuberculin sensitiveness is still undecided. It may be that this affection is related to tuberculides, the result of an abortive dissemination of tubercle-bacilli; or it may possibly be a question of irritative phenomena produced by the tuberculin content of the tissue-fluids, such as the nasal and conjunctival secretions. Moro and Doganoff and Escherich are inclined to accept the latter view but have not succeeded in proving the presence of tuberculin in these fluids. It

**Lymphatic
Constitution.**

must be mentioned, however, that Escherich (*loc. cit.*) and Moro¹⁰¹ deem it necessary to assume that tuberculin sensitiveness, as seen in scrofula, is only developed on the basis of an inborn so-called "lymphatic" diathesis. They deduce this from the fact that skin-changes of the same type as scrofula occur even in children who are not sensitive to tuberculin and that this lymphatic constitution is present during the early life of children who will later develop scrofula but are not yet tubercular nor sensitive to tuberculin. Moro thus describes lymphatism as the soil on which a chance tubercular infection leads to the development of scrofula.

If this is so, we must certainly inquire what this lymphatism or lymphatic diathesis really is. It has been recently described by Czerny as an "exudative diathesis," a disposition to torpid inflammatory processes. Correct as the idea may seem, it is unfortunately a mere paraphrase which carries us no further. It seems to me that an explanation of the cause of this exudative

**Lymphatism a
Condition of
Hypersensitive-
ness to Bac-
terial Toxins
in general.**

diathesis may be drawn from the discoveries of Moro and Escherich. They state that scrofula is really nothing more than a form of this exudative diathesis, complicated by hypersensitiveness to tuberculin, and that the diathesis precedes the scrofula in the majority of cases. The causal explanation is therefore this — that “exudative diathesis” or lymphatism is simply a condition of hypersensitiveness to bacterial toxins in general. The modern theory of hypersensitiveness to bacteria and of allergia points to the following assumption: that such a hypersensitiveness to bacteria (presumably, on Wolff-Eisner’s theory, caused by lysin) is partly inborn but can also be developed when certain bacteria, non-immunizing but causing hypersensitiveness, act in a certain degree of virulence on an organism of definite capacity for resistance. To this group of bacteria probably belong most of the noxious organisms which stimulate inflammation, such as staphylococci, streptococci, and pneumococci. In this connection, I should like to refer to what was said on p. 154 with regard to the relapses in erysipelas, articular rheumatism and pneumonia and point to the analogy between the lymphatic or scrofulous changes and the swollen face or enlarged legs of a patient suffering from chronic recurring erysipelas. The similarity of these conditions, which clearly have a natural relationship to each other, must be admitted. That this hyper-

sensitiveness to bacterial toxins is not merely present in the skin, which is directly exposed to bacterial action, but is also shared by the lymphatic glands and vessels, is clear from the intimate functional relationship of these organs with the inflammatory processes taking place within their sphere of influence. It is also easy to realize that

in such lymphatic individuals, when a tubercular infection takes place, hypersensitiveness to tuberculin and tuberculinolysin action are added to the general sensitiveness to bacterial protein. For this is only a special case of general sensitiveness to bacterial toxin. That sensitiveness to tuberculin only occurs when tubercle-bacilli have acted on the body, is clear from the law of the specificity of such phenomena. It is quite natural that just those individuals are disposed to specific hypersensitiveness to tuberculin who are sensitive to bacterial proteins in general, since bacterial proteins have certain common properties, *e.g.*, of finding similar receptors in the organism. The latter fact is illustrated by the well-known experience that bacterial proteins, each and all, have the common property of producing inflammation. I believe, then, that there is a definite connection between the lymphatic constitution, equivalent in my mind to sensitiveness to bacterial protein in general, and scrofula, which is the sign of hypersensitiveness to tuberculin in particular. This theory should, at any rate, stimulate further research and provides some explanation of the cause of scrofula. It has the additional advantage of being capable of direct proof and I hope, in the near future, to undertake this.

**Connection of
Lymphatism
with Status
Lymphaticus.**

The following interesting question will arise: Is there any intimate connection between lymphatism in this sense and the so-called status lymphaticus in the sense of Paltauf (consisting of hypertrophy of the lymphatic tissues, such as enlargement of the thymus and spleen) as is suggested by their similarity of name and common relations to the system of lymphatic glands? I believe there probably is. The extraordinary lack of resistance

to infections, and unfavourable course when infected, is a clinical parallel of the status lymphaticus, as is seen on the *post-mortem* table. This strongly points to the status lymphaticus (Paltauf) being an abnormal sensitiveness to bacteria, a hypersensitiveness which exceeds the optimum degree for defensive reactions.

Lastly, it should be mentioned that Wolff-Eisner ascribes the periodical hectic fever and falls of temperature, and also the hectic sweats of phthisical patients, to the tuberculinolysis resulting from hypersensitiveness. He

**Intermittent
Fever due to
Tuberculinolysis.**

assumes that it is a question of lytic actions on the tubercle-bacillary products reaching the blood from the tubercular foci. He also suggests that the rises of temperature in the phthisical caused by body movement depend on the fact that by the movement the blood-supply of the foci is increased, tuberculin absorbed in larger quantities, and lysinized in the blood. To carry the idea further, I believe that the high and abnormally low temperatures and hectic temperature curves result from the fact that bacillary protein in moderate doses causes rise of temperature, and in larger quantities fall of temperature. In the periodicity of these phenomena, it is probable that the normal daily fluctuation plays a part. This daily fluctuation is possibly influenced not only by absorption of toxin, but also by lysin-production.

TREATMENT OF TUBERCULOSIS IN GENERAL (SURGICAL TREATMENT)

AND TUBERCULIN TREATMENT IN THE LIGHT OF THE LYSIN THEORY.

The lytic theory of the pathology of tuberculosis and the standpoint we have taken throw light on many

questions of the general treatment of tuberculosis and tuberculin treatment.

With regard to the general therapy of tuberculosis, the following fact should be noticed, a fact which has up

to now been scarcely intelligible; after
Result of surgical removal of large tubercular foci,
Extirpation the remaining foci show more favourable
of Foci; prospects of cure than before. The best

known and most striking example is the healing of
 tuberculosis of the bladder after extirpation of a kidney
 with extensive tuberculosis. This experi-

Explained by ence can be explained as follows: the
Lysin Theory. removal of the large focus, which previously
 absorbed both lytic and antitoxic antibodies,

leaves free an amount of these protective substances
 sufficient to exert a favourable influence on the remaining
 smaller foci and promote their healing. In addition, the
 removal of the surcharge of toxin can, in itself, exert
 such a favourable influence on the general condition that
 the outlook for the patient is improved in every way by
 the operation, although it is not radical. These clinical
 facts are borne out in the researches of Bahr^{dt}.¹⁰² He
 discovered that in tubercular guinea-pigs, the tuberculin
 sensitiveness is immediately diminished by the removal
 of a part of the tuberculous tissue (especially the tissue
 first damaged by the disease); this is shown by the fact
 that the animals are less easily killed by subsequent
 tuberculin injections.

The fact is well known that the extirpation of tuber-
 cular lymphatic glands is in some cases well borne, but
 in others causes a spreading of the disease.

Result of This, too, is easily explained on the lysin
Removal of theory. In the first case, the protective
Tubercular lytic action and hypersensitiveness of the
Glands.

organism are so powerful that any tubercle-bacilli disseminated by the operation are easily rendered innocuous, as in the superinfection of tubercular guinea-pigs. In the second case, on the contrary, the non-activity of the disease renders the lytic actions insufficient to resist the dissemination of the bacilli. The theory points to the assumption that the latter event is likely to occur in cases of quite stationary glandular enlargements. These con-

**Necessity for
Cutaneous
Test before
Operation.**

siderations show the necessity of performing a cutaneous test before undertaking such an operation, and of only removing the glands when the result is definitely positive, and the lytic action therefore sufficient. Similar considerations hold for the removal of a tubercular testicle. On account of the frequency of spontaneous cure and the danger of spreading the disease (at any rate to the vas deferens), the operation should not be lightly undertaken.

Little need be said about tuberculin action in tuberculin treatment, as the most important therapeutic standpoints have been put forward in the

**Antibodies in
Tuberculosis.**

Practical Part. A few questions of therapy, however, still remain for consideration from a theoretical point of view.

The question of antibodies in tuberculin treatment has been discussed in some detail. In the first place, we have seen the existence of an antibody to the tuberculin itself — the antituberculin of Wassermann : we have seen that this is not an antitoxin but a lysin, an amboceptor of the nature of a bacteriolysin — tuberculinolysin. We have also recognized the action of true antitoxic substances. It is clear that such toxin-binding substances must necessarily play a part both in the natural cure of tuberculosis and also in a tuberculin cure, as the following considerations will show.

We have realized the value of lytic action, which is the first result both of natural tuberculin absorption and tuberculin treatment. We have seen that by means of lysin, the curative hypersensitiveness to living tubercle-bacilli is produced. Lytic action converts the tuberculin of the tubercle-bacilli into a highly toxic substance which stimulates the healing reactions; this acts as a protection to the organism, as is proved by Koch's fundamental experiments on guinea-pigs (*cf.* p. 149) and the observations of Römer on the course of a tubercular infection in cows immunized by von Behring's method. It is self-evident that this reaction due to hypersensitiveness does not itself produce a cure, but that a cure can only take place when these reactions, caused by toxic action, are finally rendered innocuous. After an inspection of Römer's temperature charts of immunized cows, which only overcome the disease by means of the most violent attacks of fever, it is impossible to doubt that antitoxic actions are in progress. This term must here be understood in its widest sense, as it is a question of the production of substances which either satisfy the affinities of the toxin (*i.e.*, the lysinized tuberculin) or further decompose or destroy it by chemical and probably fermentative processes. We have already seen in the practical part that these antitoxic actions are not all necessarily of a specific nature. The inflammatory tissue-changes show that the products of inflammation—leucocytes, lymphocytes and albuminous bodies contained in the inflammatory exudate—neutralize the toxin which has caused the inflammation; further, the cellular elements of the inflammation destroy the toxin by fermentative means and by their own metabolism; lastly, the rich

Proofs of Existence of True Antibodies.

Non-specific Antitoxic Actions.

blood supply in the inflamed part carries off the local toxin into the general circulation, where it can be destroyed by metabolic processes. All these events might be called

**Specific
Antitoxins.**

the non-specific antitoxic functions of inflammatory tissue-reactions. There is, however, no argument against the assumption that there are also antitoxins which are real specific antibodies of the lysinized tuberculin produced by means of immunization. These, it should be specially noticed, are not antitoxins of the tuberculin as such, which we have seen to be hardly a toxin at all, but of the lysinized tuberculin. As in some other infectious diseases (*e.g.*, pneumonia, streptococcal infections, typhoid), so in tuberculosis there is the objection that the presence of such antitoxic substances in the serum of previously treated animals has not been proved so definitely as in the case of exotoxic infections such as diphtheria and tetanus. The proof of the antitoxic

Maragliano.

action of tubercle-immune sera are, at any rate, somewhat unconvincing. Maragliano has asserted that his antitubercular serum annuls the toxic action of tuberculin; other workers, however, have only partially confirmed his statements. Beraneck found that although the

Beraneck.

serum of a horse treated with his tuberculin diminished the toxicity of his tuberculin in the guinea-pig as far as danger to life was concerned, it increased the power of his tuberculin to produce fever. This was probably due to the lysin con-

Grüner.

tained in the immune serum (passive transference of hypersensitiveness?). Grüner¹⁰³ used a mixture of Marmorek's antitubercular serum and tuberculin to produce cutaneous and intracutaneous reactions, but came to the

conclusion that there was probably no difference between the action of this mixture and tuberculin alone. On the other hand, the experiments of Pickert and Löwenstein (p. 127) must be taken into account. Employing the cutaneous test, they claim that the serum of slight cases, especially those that have undergone tuberculin treatment, has an antitoxic action. It should also be noticed that Schläpfer¹⁰⁴ has found that the cutaneous reaction diminishes in intensity during the course of tuberculin treatment.

I have myself made similar observations, all of which point to the probability that under the influence of therapeutic tuberculin action, true immunizing actions of an antitoxic nature take place. It is true that these positive experiences are less convincing than the very definite antitoxic actions of diphtheria and tetanus-immune serum. The negative or indefinite results of the tests on tuberculin-immune serum with respect to its antitoxic action, are, however, what would be expected, as the following considerations will show. Firstly, according to my conception, a tubercle-immune serum must also contain lysin, as is proved by the possibility of a passive transference of tuberculin sensitiveness by the serum.¹⁰⁵ Therefore complete neutralization of the tuberculin action by a tubercle-immune serum cannot be expected, as its antitoxic actions are sometimes more than counterbalanced by the lysin, which produces a toxin from the tuberculin. Thus the conditions are more complicated than in the case of diphtheria or tetanus. In addition, it is quite arbitrarily assumed by those who test such sera, that the antitoxic substances must be present in considerable concentration. This need by no means be the case with

**Reasons for
Indefinite
Results of Tests
on Tuberculin
Immune Serum.**

a tubercle-immune serum, as in diphtheria and tetanus. It is quite conceivable that antitoxic substances are present in the serum in considerable amounts; the concentration, however, may be such that although they can prove highly active (since the whole blood-stream bathes the foci), the small quantity of serum tested against antigen may contain insufficient antitoxin to give a positive result. In addition to the experiments

of Pickert and Löwenstein, and Maragliano and Beraneck, which speak for the existence of a true tuberculin antitoxin, the researches

**Opsonic Action
annulled by
Tuberculin.**

of Manaud¹⁰⁶ are of importance: he has

discovered that the opsonic action of serum on tubercle-bacilli can be annulled by the addition of tuberculin. This fact is most easily explained by assuming that the tubercle opsonin of the serum is an antitoxin of the (lysinized?) tuberculin, with which it combines and becomes inactive. Wright's opsonic experiments, too, are an argument in favour of the existence of antitoxins in tuberculosis; for the opsonin—which prepares the tubercle-bacilli for ingestion by the leucocytes—must surely be considered as a kind of antitoxin, since Wright has shown that the opsonic action is directed to the tubercle-bacilli and is not, for instance, a stimulation of the leucocytes. The consideration that the

**Antitoxins of
Endotoxic
Diseases chiefly
present in the
Foci.**

difficulty of proving the presence of antitoxins is no evidence of their absence, may also be applied to other hypothetical antitoxins, as in pneumococcal and strepto-

coccal infections, which are both cases of endotoxic, not exotoxic actions. It should be noticed that in all endotoxic diseases, of which tuberculosis is one, it is highly probable that the antitoxic substances play their part chiefly in the foci and possibly remain there, as the

endotoxins chiefly act locally on the tissue-cells. Therefore, no flooding of the blood by antitoxins takes place as in the case of diphtheria and tetanus, where their presence in the serum can be proved, because the organism has not undergone any phylogenetic development to such a useless function.

All these endotoxic diseases are characterized by the fact that the fight against the infection is essentially a local one, taking place in the tissues. Tuberculosis is a typical endotoxic disease and a characteristic example of such a local fight. When we see how frequently a tubercular focus in one place will heal while a new focus is formed in another situation (occurrence of pulmonary tuberculosis just after the complete healing of a tubercular focus in a bone, laryngeal tuberculosis in cases of healed pulmonary tuberculosis, &c.), we are forced to conclude that the healing process in tuberculosis is essentially a local event. The process by no means suggests healing by means of humoral factors of immunity. This tallies with the view expressed on p. 151 that the apparent immunity produced in cows by weakened tubercle-virus is not a true immunity in the old sense, but rather an immunity due to hypersensitiveness which explains the fact that these immunizing experiments on cows are not always successful. Other endotoxic diseases such as pneumonia, erysipelas, and articular rheumatism are quite analogous to tuberculosis in respect of immunity. The manner of incidence of these affections does not suggest any real immunity. They arise in the same way as tuberculosis and the formation of new foci after healing of the primary focus (streptococcal abscesses after healed erysipelas, empyema after healed pneumonia, spreading of articular rheumatism from joint to joint, persistence of endocarditis after healing of articular rheumatism, &c.) points to the decline of the general defensive forces in the local fight waged by the tissues against the toxin causing the disease.

In spite of the uncertain results of experimental research, and of serum treatment of tuberculosis, such considerations prove the existence of an anti-toxin in tuberculosis, which must be reckoned with in the treatment of the disease; this the more as some positive results have attended the attempts to prove its existence.

**Proofs from
Tuberculin
Treatment of
a Specific
Antitoxin.**

The very fact that progressive tuberculinization can produce marked insensitiveness to tuberculin is also a probable indication of the existence of specific antitoxins to lysinized tuberculin. The increase of lysin, proved by Wolff-Eisner and by the hypersensitiveness occurring when the dosage exceeds the level of tox-immunity, naturally does not itself explain the insensitiveness. On the contrary, if antitoxin production did not take place parallel with lysin formation, the hypersensitiveness to tuberculin (both as regards focal and general reactions) caused by the increasing lytic action, would correspondingly increase rather than diminish.

This conception could be simplified by assuming that the toxic actions of lysinized tuberculin possibly only represent an intermediate stage in the katabolism of tuberculin. The antitoxic action, then, occurs because the final and complete lytic action produces non-toxic decomposition products, just as toxic products (albumoses and peptones) arising during the digestion of genuine albumin, are finally converted into non-toxic substances (amino-acids). In this simplified conception, the lysin, as regards its ultimate action, is not an "antitoxin" which annuls the toxic action by combining with the toxin, but rather an "antitoxin" which decomposes the toxin by lytic action, a ferment which, possibly in conjunction with complement, first increases the toxicity of the tuberculin, then destroys it. The idea is, however, purely hypothetical, and I do not desire to press it; this the more since, on such a hypothesis, it is difficult to understand why, in individuals who possess acquired immunity to tuberculin, there has been no sign of even temporary toxic actions, corresponding with an intermediate stage in the decomposition of the tuberculin.

We can now define the action of tuberculin treatment as follows : Under the influence of progressive doses of tuberculin, the action of the lysin or amboceptor is increased. This has the advantage that bacteriolysis takes place and that irritative actions of an immunizing nature are produced in the foci by means of the lysinized tuberculin.

Toxic Action of Lysinized Tuberculin an Intermediate Step.

Definition of Tuberculin Action.

The antitoxic action is, however, increased in still higher proportion (of course in favourable cases only); therefore all manifest signs of reaction, which would otherwise result from lytic action, can be completely avoided by careful tuberculin dosage.

The explanation of deferred reactions on the lysin theory has a practical bearing on tuberculin treatment.

These deferred reactions can only be explained by assuming the presence of a certain degree of tuberculin sensitiveness, *i.e.*, after tuberculin injection, a certain excess of lysinized tuberculin over the antitoxin contained in the blood, but that this excess is not a large one: therefore the clinical actions of the lysinized tuberculin take place but slowly, owing to the anti-action of the antitoxin. Such deferred reactions, although they undoubtedly give warning of a surcharge of toxin, are not to be feared to the same extent as more immediate reactions. Therefore, in such cases, the reduction of dose need not be so great as in immediate reactions.

Beraneck¹⁰⁷ has proved (*cf.* p. 122) that not only tuberculin but also antituberculin serum (prepared for experimental purposes by this author) has the power of weakening the virulence of tubercle-bacilli; this fact is also of importance with regard to tuberculin treatment. This property of Beraneck's antituberculin serum points to the fact that the lysin of the tuberculin, which is of the nature of a bacteriolytic amboceptor, has not only a lytic action on the endotoxin, but also, like a true bacteriolysin, a destructive action on the vitality and intimate cellular structure of tubercle-bacilli. It may not be possible to prove that the serum will directly dissolve up tubercle-bacilli

**Deferred
Reactions.**

**Lytic Action
on Tubercle-
bacilli;
Beraneck.**

in a test-tube, but I have not heard of any experiments in this direction. Similarly, Marmorek¹⁰⁸

Marmorek.

found that a young culture of tubercle-bacilli treated with his antitubercular serum is absorbed by the subcutaneous tissue of rabbits almost without reaction, while tubercle-bacilli treated with ordinary horse serum caused abscesses. It was undecided whether this was due to true bacteriolysis by means of the lysin contained in the immune serum or whether it was just a weakening of the virulence of the bacilli. A weakening of tubercle-bacilli by serum containing lysin probably occurs in Marmorek's experiments with tubercular guinea-pigs (*cf.* p. 158).

Although I have shown that antituberculin serum has bactericidal and antitoxic properties, it does not follow that I consider such sera suitable for the treatment of tuberculosis. On pp. 105-106 are given the grounds on which I consider that little can be attained by the serum treatment of tuberculosis.

We have seen that the increasing insensitiveness to tuberculin of patients undergoing tuberculin treatment is clearly not a real insensitiveness but merely a cloak hiding an increasing humoral hypersensitiveness, due to lytic action, with the simultaneous production of larger and larger amounts of antitoxic substances. Therefore, since hypersensitiveness must be recognized as the most important defence against tuberculosis, Wolff-Eisner's¹⁰⁹ objection to tuberculin treatment on the ground that such insensitiveness is a barrier to therapy, falls to the ground.* The experience that, in spite of an increasing apparent insensitiveness to tuberculin, good results are

* As Wolff-Eisner is really a believer in tuberculin treatment, he can only make this statement in the rôle of an *advocatus diaboli*!

obtained in tuberculin treatment, can only be made to agree with the established value of hypersensitiveness by assuming the presence of antitoxic actions, hiding the hypersensitiveness.

The lysin theory affords an explanation of the fact that the very cases which are highly sensitive to tuberculin often make most progress with tuberculin treatment, of course with small doses.

**Good Results
in Cases highly
sensitive to
Tuberculin.**

This depends on the high capacity of such cases for reaction, by means of which the tuberculin injections produce large amounts of lysin, causing powerful stimulation of the natural healing factors and the specific antitoxic actions. It is quite conceivable that these cases might be recognized in advance by means of a quantitative cutaneous test (*cf.* p. 147).

In closing this theoretical consideration of the treatment of tuberculosis, one further point must be noticed.

We have seen that tuberculin in itself is but feebly toxic for the healthy, and only displays its toxic action when introduced into a tubercular body, where it becomes lysinized and stimulates the anti-actions of the organism. Landmann's objection, therefore, to Beraneck's tuberculin that it is but little toxic for the healthy guinea-pig, is illogical. Indeed, its high specificity is proved by the very fact that it is practically non-toxic for the healthy animal, but has an extraordinarily high toxicity for the tubercular organism, a toxicity which causes reactions in the human body with the very smallest doses. This consideration also confirms the view that many other tuberculins in which the difference between the toxicity for the healthy and the tubercular is smaller, contain substantial impurities in the form of unspecific harmful toxins of no value for therapy. On account of its pure

**High Specificity
of Tuberculin
Beraneck.**

specificity, apart from its convenient method of dispensation in suitable dilutions and the other grounds mentioned on pp. 117-123, I have selected tuberculin Beraneck as the most suitable tuberculin for the practitioner.

The lysin theory gives a good explanation of the phenomenon that the toxicity of tuberculin for the healthy animal bears no fixed proportion to its toxicity for the tubercular organism; therefore the standardizing of tuberculins by finding the lethal dose for the healthy guinea-pig, as advocated by Landmann, cannot be justified. The point has been emphasized on pp. 119-120.

**Standardiza-
tion of
Tuberculin.**

THE PROBLEM OF IMMUNIZATION AGAINST TUBERCULOSIS BY TUBERCULIN IN THE LIGHT OF THE LYSIN THEORY.

We must now consider the following remarkable fact—that no complete immunity to tuberculosis can be obtained by previous tuberculin treatment, and that on this account it has been impossible to replace the tuberculin treatment of early tuberculosis by a protective tuberculin treatment of the still healthy individual. This is the more striking when it is realized that von Behring¹¹⁰ has succeeded in immunizing cattle against tubercle virus, highly virulent and fatal for control animals, and this by means of the injection of human tubercle-bacilli of low virulence (*cf.* p. 151). If the action of living tubercle-bacilli is equivalent in every respect to local and general tuberculin action; if the immunity of von Behring's cattle and the phenomena of immunity in the superinfected guinea-pig both depend on hypersensitiveness to the tubercle-bacilli;* if this hypersensitiveness is caused by the lysin-content of the organism which produces a toxin

**No Complete
Immunity by
means of
Tuberculin
Treatment.**

* *Cf.* pp. 148-151.

from the bacilli; if the active substance of the tubercle-bacilli is really tuberculin, as we have assumed; lastly, if the lysin of the tubercle-bacilli is also the lysin of the tuberculin, then it seems only natural that immunity to tuberculosis could be obtained not only by injection with living tubercle-bacilli of lowered virulence, but also by purely chemical tuberculin action. Now there is no doubt that in animals a certain limited degree of immunity can be attained by previous tuberculin treatment. The most satisfactory results in this connection have been obtained by Beranek¹¹¹; he treated guinea-pigs with his tuberculin before artificially infecting them, and thereby considerably prolonged their lives. In the end, however, the animals died of tuberculosis. This

Does Tuberculin contain the True Tubercle Toxin?

impossibility of obtaining complete immunity to tuberculosis by means of tuberculin has raised a doubt whether in tuberculin we really possess the active principle of living tubercle-bacilli, and whether Wolff-Eisner's lysin theory can be applied both to the living tubercle-bacillus and to tuberculin. I believe, however, that these doubts are unjustified, and that the differences between the immunizing action of living tubercle-bacilli and dead tubercle-bacillary substance can be explained, even though it is true that the toxic substance is the same in both, and the lysin theory is applicable to both.

Working on the assumption that the phenomena of immunity, seen in Koch's superinfection experiments,

Difference in Action between Living Tubercle-bacilli and Tuberculin only one of degree.

and in Behring's immunized cattle, are connected with hypersensitiveness, the difference between the action of tuberculin and living tubercle-bacilli is seen to be that with the latter pronounced signs of hypersensitiveness can be easily produced (Koch's funda-

mental research in superinfection), but with the former only in a lesser degree. So in a correct tuberculin cure, although the gradually rising dosage corresponds in its chemical action in some measure with the progressive disease, caused by living tubercle-bacilli, no signs of hypersensitiveness are usually observed; rather the reverse, as larger and larger doses of tuberculin are tolerated without reaction. Thus, too, a healthy animal treated with tuberculin does not show the characteristic reactions due to hypersensitiveness when subsequently infected with tubercle-bacilli, as does the tubercular guinea-pig in Koch's experiment. At first sight it might be concluded that the tuberculin does not produce any hypersensitiveness; in this case, the whole doctrine of hypersensitiveness (as seen in immunized animals and in the phenomena of immunity on superinfection) caused

Proved by Production of Tubercles by Tuberculin.

by the action of tuberculinolysin, could scarcely be maintained. As it is, however, the identity of the chemical action of tubercle-bacilli and of tuberculin is definitely proved by the demonstration that anatomical tubercles can be produced by tuberculin (*cf.* p. 113). In addition,

Wolff-Eisner.

Wolff-Eisner¹¹² has shown that animals can be rendered hypersensitive by repeated injections of comminuted tubercle-bacilli, so that they die after a number of such injections.

He therefore concludes that between the action of the chemical preparations of tubercle-bacilli and the living organisms themselves, there is no difference in principle but only in degree. His statement that hypersensitiveness can be produced by previous treatment with dead tubercle toxin is, it is true, opposed to the views of other authors. For this reason, I have gone into the question in my clinic, using tuberculin Beraneck. My assistant,

Dr. Stocker, has just published the results of the research in his treatise on "The Production of Hypersensitiveness to Tuberculin Beraneck."¹¹³ He

**Stocker's
Experiments.**

injected moderate doses (2 c.c. of the concentrated tuberculin Beraneck) into

guinea-pigs, thereby obtaining a certain degree of hypersensitiveness, evidenced, on the second injection after fourteen days of 5 c.c. of the same tuberculin, by the death of the animals which normally easily tolerate 7 c.c. It is true that this is not a very high degree of hyper-

**Hypersensi-
tiveness in
Tuberculin
Treatment.**

sensitiveness. At all events, clear signs of hypersensitiveness are sometimes apparent in tuberculin treatment; for example, after a period of good tolerance of the

rising doses a time may suddenly come when no further rise is tolerated, or reactions may even occur to much smaller doses, previously well borne; it is clear, that in such cases hypersensitiveness to tuberculin has unfortunately occurred. It must, of course, be admitted that the living tubercle-bacilli of the patient may have something to do with this. However, it

**Hypersensi-
tiveness in
Conjunctival
Test.**

must be remembered that if the conjunctival test be repeated several times on the same patient, a purely local hypersensitive-

ness of the conjunctiva may occur, a hypersensitiveness quite independent of the action of living tubercle-bacilli. Wolff-Eisner therefore states that a positive result of the conjunctival test can only be considered definite proof of active tuberculosis when obtained at the first trial, which should therefore not be repeated. However,

**The Difference
not Explained
on the Side-
chain Theory.**

in spite of these examples, the signs of hypersensitiveness after tuberculin are, as is proved in the normal course of a reactionless tuberculin treatment, by no means equivalent to

those produced by a tubercular infection, and this fact seems to be closely connected with the impossibility of a complete immunization of animals by means of tuberculin. Wherein, then, lies the difference? Assuming the identity of tuberculin and tubercle-bacillary substance, it is hardly possible that the healthy animal in which immunization with tuberculin is attempted, should lack the receptors necessary for lysin production; for, if this were so, from whence would the organism obtain the receptors essential for acquiring the infection?

The very possibility of a reactionless tuberculin treatment provides a satisfactory explanation of the difficulty.

Difficulty explained by the possibility of a Reactionless Tuberculin Treatment. We have seen that reactions, if present at the commencement of treatment, gradually subside or in other cases do not appear at all. This has been explained by the fact

that the tuberculin, in such a progressive treatment, is lysinized in increasing amounts, while the reaction due to hypersensitiveness, which would otherwise occur in proportion to the amount of this lysinized tuberculin, is kept back by the antitoxic actions of the organism. By this means, the hypersensitiveness is masked, only being present in the form of increased lytic action and never being clinically perceptible. This is, of course, fortunate for treatment, as otherwise a successful tuberculin cure would probably be impossible.

A Masked Hypersensitiveness and Tox-immunity detrimental to Immunization. A masked hypersensitiveness is, however, naturally a great obstacle in the way of immunization by means of tuberculin, as in immunization the chief factor is the actual hypersensitiveness, with its prompt inflammatory and bacteriolytic anti-actions. For no other immunity to tuberculosis is yet known but that due to reactive hypersensitiveness. Thus it is quite intelligible that complete

immunity by means of tuberculin cannot be obtained, at any rate with the present technique. The obstacle is the very thing that is aimed at in treatment in the interests of the patient, *i.e.*, tox-immunity to lysinized tuberculin. In Koch's previous treatment with living tubercle-bacilli (an immunizing infection with tubercle-bacilli of low virulence), such a tox-immunity naturally does not take place; herein lies the difference as regards immunizing action. This is evidenced by the clinical phenomena both in Koch's experiments and in von Behring's immunization of cattle. In the former, the absence of tox-immunity of the infected and superinfected guinea-pig is at once evident by the immediate inflammatory reaction to the superinfection. In the case of von Behring's cattle, immunized by vaccination with living tubercle-bacilli, the absence of tox-immunity, in spite of the fact that they successfully resisted the first infection, is shown by the acute febrile phenomena produced by the second infection before they can definitely throw it off.

These considerations clearly point to the distinct difference between real immunization and an immunizing treatment, a difference that Landmann does not acknowledge. We are bound to recognize a certain antithesis between tuberculin treatment (an immunizing healing action) and true immunization. The former consists only of small immunizing actions, but includes tox-immunity, which is of importance for therapy. Immunization with living tubercle-bacilli, on the other hand, causes no tox-immunity, and for this very reason it produces immunity by making complete use of the lytic action, by actual reactive hypersensitiveness.

The following, then, is the real difference between

**Absence of
Tox-immunity
in Koch's and
Behring's
Experiments.**

**Antithesis be-
tween Tuber-
culin Treat-
ment and true
Immunisation.**

living tubercle-bacilli and tuberculin. We have already seen that in tuberculin treatment the tuberculin is applied so to speak in jerks in the form of temporary inundations of the organisms, while in the action of living tubercle-bacilli there is a regular and unbroken supply of toxin ; this probably explains the difference of action. For it is quite conceivable that in the tuberculin injections used for immunization the repeated variations of concentration of the toxin cause a larger production of antitoxin than is the case in an immunizing infection with tubercle-bacilli, when such variations do not occur ; and this antitoxin production is a barrier to the formation of a certain measure of actual hypersensitiveness, which is necessary for immunity.

The difference, then, between the action of living tubercle-bacilli and previous tuberculin treatment in respect of immunity depends on the fact that in one case gradual tuberculin actions take place, in the other sudden tuberculin actions. This explanation is borne out by the observation of Heymans,¹¹⁴ who succeeded in rendering animals sensitive to tuberculin, and immunizing them against living tubercle-bacilli by placing living tubercle-bacilli in their bodies in collodion sacs. From these sacs, the soluble toxins are diffused and absorbed without the occurrence of a tubercular infection, although the neighbouring tissues undergo tubercle-like changes due to the purely chemical action of the substances diffused through the sacs.

This, however, is not the only explanation possible. It may be that the production of the substance causing the protective hypersensitiveness to living tubercle-bacilli—the lysin—is not sufficiently stimulated by the tuberculin

**Gradual v.
Sudden Toxic
Actions.**

Heymans.

as such, but that the lysin is chiefly or entirely elaborated in the anatomical tubercular foci from the tissue-cells under the influence of the tuberculin which is contained both in the tubercle-bacilli in the foci and in the circulating blood. Thus the formation of lysin chiefly takes place in an organism with tubercular changes and not in the healthy body. This conception is borne out by the experiments of Bahrddt, mentioned on p. 170.

Sensitiveness diminished by Removal of Tuberculous Tissue.

These showed that tuberculin sensitiveness and therefore probably also the lysin-content of the body is immediately decreased by the removal of tuberculous tissue. With this assumption, it seems possible that in Heyman's experiment the hypersensitiveness and immunity are not only caused by the slow and regular absorption of tuberculin from the collodion sacs, but also by the fact that in the neighbourhood of the sacs tubercle-like tissue is formed which may be regarded as the focus of lysin production.

We have, then, two possible explanations of the difference between the action of living tubercle-bacilli and tuberculin with regard to the production of immunity due to hypersensitiveness. In face of these possible explanations and of the fact that local tuberculin action can bring about the formation of tubercles, it is difficult to justify the frequent assertion that in tuberculin we do not possess the real tubercle-toxin.

Tuberculin contains the real Tubercle Toxin.

It must be acknowledged, however, that Römer,¹² one of the most competent research workers in immunity to tuberculosis, both in his earlier and more recent publications, has stated his conviction that between the action of tuberculin and living tubercle-bacilli there is a differ-

ence not only of degree but also in principle. The gist of his argument is this: that cattle immunized by living tubercle-bacilli and normal animals both show about the same sensitiveness to tuberculin, while the immunized animals show a high degree of hypersensitiveness to tubercle-bacilli as a sign of their immunity, which is not the case with the control animals. However, in face of the strong reasons which have been given to demonstrate the identity of the chemical action of living tubercle-bacilli and tuberculin and the presence of the true tubercle-toxin in the latter, it seems to me that Römer's arguments ought not to be overestimated. For, with regard to the absence of hypersensitiveness to tuberculin in his immunized cattle, the following considerations arise: the immunized animals have, by virtue of their previous treatment with weakened tubercle virus, become capable of bringing reactions due to hypersensitiveness to bear on the infection with living tubercle-bacilli. Now although these reactions are to be considered as lytic actions, it by no means follows that the immunized cattle command a large store of previously formed lysin at the time of the test. It is sufficient to assume that the previous immunizing treatment has rendered the animals capable of producing lysin if need be at any given moment. Now it is quite credible that just as tuberculin injections alone do not easily produce hypersensitiveness in the non-tubercular organism, so also in the testing of immunized cows the acquired capacity for reaction and the hypersensitiveness are only manifest when living tubercle-bacilli are employed; for these alone cause the specific and lasting local damage to the tissues, which in non-treated animals causes the

Römer claims a Difference in Principle between Action of Tuberculin and Living Tubercle Bacilli.

Römer's Dualistic Theory unnecessary.

formation of tubercles. This it is that stimulates lysin-production. In the injection of tuberculin, however, which is quickly absorbed and causes no local irritation of a powerful and specific nature, no such lytic action nor hypersensitiveness occurs, even in previously treated animals. This explanation deprives Römer's claim of a difference in principle between tuberculin and the toxin of living tubercle-bacilli of its significance, and seems definitely to contradict such a dual theory, which would enormously complicate the pathology of tuberculosis and tuberculin treatment.

Having reached a standpoint which explains the difficulties of tuberculin immunization against tubercu-

**Possibility of
obtaining Im-
munity by a
Modified
Technique.**

losis, the problem might now be approached of producing a high degree of hypersensitiveness, and therefore immunity by some suitable modification of the present technique; for this is naturally a problem of the greatest importance, especially for man. (1) It might be thought that the goal could be reached by injecting tuberculin very frequently, and avoiding variations of concentration, in imitation of the action of a tubercular infection, also producing, if possible, by means of the repeated injections, the tubercle-like tissue changes, which we have seen can arise from local tuberculin action. Experiments in this direction made by Dr. Stocker in my clinic have hitherto been unsuccessful. For this purpose, perhaps, the employment of tuberculin ointments may be specially fitted. Moro¹¹⁶ has proved that tuberculin is absorbed from a tuberculin ointment, and local changes of a tubercular nature occur in the skin.¹¹⁷ It also appears possible that tuberculin or dead tubercle-bacilli in collodion sacs might be placed in the bodies of animals, as in Heymans' ¹¹⁸ experiments with living tubercle-bacilli,

which should result in a gradual and regular absorption of tuberculin and tubercle-like changes in the neighbouring tissues, analogous to a tubercular infection. As we have seen, Heymans' method with living tubercle-bacilli succeeded in producing both hypersensitiveness to tuberculin and immunity to a tubercular infection, and it is quite possible that a modification of his technique, using dead tubercle-bacilli or tuberculin, might have a similar effect. (2) It might be possible, however, that the very antithesis of this method will attain the desired end, *i.e.*, that massive doses of tuberculin should be injected with the object in view of allowing the lytic action, essential for immunization, to get the mastery over the antitoxin formation which is detrimental to immunization. The results of Dr. Stocker's experiments in my clinic (*cf.* p. 184) with the single injection of large doses of tuberculin Beraneck, although they only indicate a low degree of hypersensitiveness, seem to show that this method of high dosage (with but a single injection) may possibly be able to produce hypersensitiveness and thereby immunity. (3) We have already considered the possibility that the lysin (causing hypersensitiveness and signs of immunity to tuberculosis) is chiefly produced by the tuberculin contained in tuberculous tissues or, at any rate, is only produced in large quantities in non-tuberculous tissue when the tuberculin acts for a considerable length of time and in similar concentration and intensity to that in tubercular foci. Dr. Stocker has therefore made experiments to determine whether hypersensitiveness and immunity can be produced with tuberculin by depositing it in the body in the form of an insoluble precipitate, which is but slowly absorbed. We had in view the possibility that in the neighbourhood of the precipitate, tubercle-like tissue will be produced, just as in the

ordinary cutaneous test. The results of these experiments have until now been negative.

In any case, with respect to any possible method of active immunization by means of tuberculin, one thing

seems quite certain—that no method can be successful which does not produce morbid symptoms in the individual, due to the lysinized tuberculin and hypersensitiveness.

**Necessity of
producing
Morbid
Symptoms.**

For the reason why previous attempts at complete immunization by means of tuberculin have been unsuccessful can only be this—that the phenomena of hypersensitiveness have been either absent or inadequate, possibly because the lysin formation has been insufficient, possibly because the protective action of the lysin has been paralysed by the appearance of antitoxic actions. It seems more than probable that immunization against tuberculosis must follow the rule of all active immunization in that it can only be obtained at the expense of morbid symptoms. For the latter are the expression of the anti-action of the organism and in previous attempts at immunization by means of tuberculin healthy animals have not generally exhibited any definite morbid symptoms.

REFERENCES.

- ¹ BERANECK. (a) "Sur les tuberculines," *Comptes-rendus de l'Ac. des Sciences*, vol. cxxxvii, No. 21, Nov. 23, 1903.
 b) "Une nouvelle Tuberculine," *Revue méd. de la Suisse romande*, 1905, No. 10, Oct. 20.
 (c) Congrès international de la tuberculose, Paris, Oct. 2-7, 1905.
 (d) "La tuberculine Beraneck et son mode d'action." Conference at the Swiss Medical Congress at Neuchâtel, May 25, 1907, *Revue méd. de la Suisse romande*, 1907, No. 20.
 (e) "Réponse à M. le Dr. Landmann" and "Quelques mots à propos de la duplique du Dr. Landmann," *Brauer's Beiträge zur Klinik der Tuberkulose*.
- ² WOLFF-EISNER. "Frühdiagnose und Tuberkuloseimmunität," Würzburg, 1909, 2nd edition.
- ³ BARTEL and NEUMANN. *Wiener klin. Wochens.*, 1906, quoted from Wolff-Eisner, *loc. cit.*, p. 170.
 MACIESKA JELŃSKA. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. viii, p. 1.
- ⁴ LICHTHEIM. (a) *Klin. Jahrbuch*, 1891, Ergänzungsband "Die Wirksamkeit des Kochschen Heilmittels," p. 634.
 (b) *Deutsche med. Wochens.*, 1891.
- ⁵ GUTSCH. *Deutsche med. Wochens.*, 1901.
- ⁶ DENYS. "Le bouillon filtré du bacille de la tuberculose dans le traitement de la tuberculose humaine," Louvain, Uytendaele, 1905.
- ⁷ SCHNÖLLER. "Theoretisches und Praktisches über Immunisierung gegen Tuberkulose," Strassburg, Schmidt, 1905.
- ⁸ NÄGELI. "Über die Häufigkeit, Lokalisation und Ausheilung der Tuberkulose," *Virchow's Archiv*, vol. clx, 1900.
 BURCKHARDT. *Zeitsch. für Hygiene*, vol. liii, 1906.
- ⁹ E. MÜLLER and PEISNER. *Münch. med. Wochens.*, 1908, No. 17.
- ¹⁰ GRUBER and KENZO FUTAKI. *Deutsche med. Wochens.*, 1907, No. 39.
- ¹¹ DUNGER. *Archiv für klin. Med.*, vol. xci, 1909, sections 3 and 4.
- ¹² METSCHNIKOFF. *Bulletins de l'Institut Pasteur*, 1909, Nos. 13 and 14.
- ¹³ PETERSON and SALIMBÉNI. *Annales de l'Institut Pasteur*, 1909, No. 7.
- ¹⁴ ROLLY and MELTZER. *Archiv für klin. Med.*, vol. xciv, 1908.
- ¹⁵ LÜDKE. *Archiv für klin. Med.*, vol. xcv, 1909.
- ¹⁶ LERMAIER. *Archives internationales de Pharmacodynamie*, vol. v, 1898.
- ¹⁷ BARANKIEFF. *Zeitsch. für klin. Med.*, vol. lxxviii, 1909.
- ¹⁸ ZIEGLER. *Cong. für innere Med.*, 1895.
- ¹⁹ NÄGELI. *Virchow's Archiv*, vol. clx.
- ²⁰ BURCKHARDT. *Zeitsch. für Hygiene*, vol. liii.
- ²¹ LANDMANN. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. x, 1908. (Beraneck's and my replies to the attack of Landmann are also to be found here.)
- ²² NÄGELI. *Archiv für klin. Med.*, 1900, vol. lxxvii.
- ²³ RÖMER (quoted). "Die Ehrlichsche Seitenkettentheorie," *Wien*, 1904, p. 68.

- ²⁴ LANDMANN. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. x, 1908. (In this book are also Beraneck's and my replies to Landmann.)
- ²⁵ BURCKHARDT. "Verhandlungen des Kongresses für innere Medizin," 1905. Discussion, p. 351.
- ²⁶ LAWSON and IAN STRUTHERS STEWART. *Lancet*, Dec. 9, p. 1681.
- ²⁷ MANTOUX. *Presse médicale*, 1910, Jan. 5.
- ²⁸ HAMBURGER. *Wiener klin. Wochens.*, 1908, No. 12.
- ²⁹ LANDMANN. *Brauer's Beiträge zur Klinik der Tuberkulose*, 1908, vol. x. (My objections to the views of this author are also to be found here.)
- ³⁰ FRIEDBERGER and MORESCHI. *Deutsche med. Wochens.*, 1906, No. 49, p. 1986.
- ³¹ JUNIUS. *Zeitsch. für Augenheilkunde*, vol. xxi, Section 5.
- DAVID. "Sitzungsberichte der medizinischen naturwissenschaftlichen Gesellschaft zu Münster" (Westphalen), June Session, 1909.
- ³² LÖWENSTEIN. *Zeitsch. für Tuberkulose*, 1905.
- ³³ NÄGELI. *Virchow's Archiv*, vol. clx, 1900.
- ³⁴ BURCKHARDT. *Zeitsch. für Hygiene*, vol. liii, 1906.
- ³⁵ HAMBURGER. *Wiener klin. Wochens.*, 1908, No. 12.
- ³⁶ RÖMER. *Brauer's Beiträge zur Klinik der Tuberkulose*, 1909, vol. xii.
- ³⁷ KREHL. *Archiv für exp. Pathologie und Pharmakologie*, vol. xxxv. KREHL and MATTHES. *Ibid.*, vol. xxxviii.
- MATTHES. *Archiv für klin. Med.*, vol. lix.
- ³⁸ JUNIUS. *Zeitsch. für Augenheilkunde*, vol. xxi, Section 5.
- DAVID. Reports of the Scientific Medical Association, Münster (Westphalia), June Session, 1909.
- ³⁹ WOLFF-EISNER. *Loc. cit.*, page 303. (Münzer also quoted from Wolff-Eisner, *ibid.*)
- ⁴⁰ BERANECK. "Sur la technique des injections de ma tuberculine dans les tuberculoses chirurgicales. Communication présentée au Congrès international de la tuberculose à Paris," 1905.
- ⁴¹ WOLFF-EISNER. "Frühdiagnose und Tuberkuloseimmunität." 2nd edition, Würzburg, C. Kabitzsch, 1909.
- ⁴² MEISSEN. *Zeitsch. für Tuberkulose*, vol. x, Section 4.
- ⁴³ DAELS. *Med. Klinik*, 1908, No. 2.
- WOLFF-EISNER. *Loc. cit.*, p. 130.
- KLINGEMÜLLER. *Ibid.*, p. 130.
- ⁴⁴ ZIELER. *Münch. med. Wochens.*, 1908, No. 32, p. 1685.
- PICK.
- ⁴⁵ SIEGRIST. *Therap. Monatshefte*, April, 1908.
- ⁴⁶ ZIELER. *Münch. med. Wochens.*, 1908, No. 32, p. 1685.
- ⁴⁷ WOLFF-EISNER. "Frühdiagnose und Tuberkuloseimmunität," Würzburg, 1909.
- ⁴⁸ DEUTSCH and FEISTMANTEL. "Impfstoffe und Sera," Leipzig, 1908.
- ⁴⁹ LANDMANN. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. x, 1908.
- ⁵⁰ BERANECK. Address at the Swiss Medical Congress at Neuchâtel, May 25, 1907; and in the *Revue médicale de la Suisse romande*, No. 6, June 20, 1907.
- ⁵¹ BERANECK. "Sur la technique des injections de ma tuberculine dans les tuberculoses chirurgicales." Communications présentées au Congrès international de la tuberculose à Paris, 1905.
- ⁵² WOLFF-EISNER. *Loc. cit.*, 2nd edition, p. 208.
- ⁵³ PICKERT and LÖWENSTEIN. *Deutsche med. Wochens.*, 1908, No. 52.
- PICKERT. *Deutsche med. Wochens.*, 1908, Nos. 23 and 25.
- ⁵⁴ NÄGELI. *Virchow's Archiv*, vol. clx.
- BURCKHARDT. *Zeitschr. für Hygiene*, vol. liii.
- ⁵⁵ O. HERTWIG. "Über die physiologischen Grundlagen der Tuberkulinwirkung," Jena, 1891.
- ⁵⁶ WOLFF-EISNER. *Loc. cit.*, p. 246.

- ⁵⁶ WASSERMANN and BRUCK. *Deutsche med. Wochensch.*, 1906, No. 12.
- ⁵⁷ STRAUSS and WEIL. *Wiener klin. Wochensch.*, 1908, No. 29, quoted from Wolff-Eisner, *loc. cit.*, p. 248.
- ⁵⁸ WOLFF-EISNER. *Loc. cit.*, p. 249.
- ⁵⁹ COHN. *Berliner klin. Wochensch.*, 1908, No. 28.
- ⁶⁰ CZASKA. *Wiener klin. Wochensch.*, 1908, No. 26.
- ⁶¹ WOLFF-EISNER. *Loc. cit.*, p. 250, gives arguments in support of this.
- ⁶² COHN. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. xi.
- ⁶³ WOLFF-EISNER. *Zentralblatt für Bakteriologie*, vol. xxxvii, sections 3, 4 and 5; *Berliner klin. Wochensch.*, 1904, Nos. 42-44.
- ⁶⁴ ARTHUS. *Soc. de Biologie*, 1903.
- ARTHUS and BRETON. *Ibid.*
- THEOBALD SMITH. *Journal of Medical Research*, 1905, vol. xxii.
- VON PIRQUET. "Die Serumkrankheit," Wien, 1905.
- ⁶⁵ VON PIRQUET. "Klin. Studien über Vaccination und vaccinale Allergie," Wien, Deuticke, 1907.
- ⁶⁶ VON PIRQUET. *Berliner klin. Wochensch.*, 1907, 20, 22; *Med. Klinik*, 1907, 40. For further literature, cf. the Essay by von Pirquet on "Allergie" in the *Ergebnissen der inn. Medizin und Kinderheilkunde*, 1908, vol. i.
- ⁶⁷ EBER. *Zeitsch. für Tiermedizin*, vol. xxi, 1895.
- ⁶⁸ ABDEHOLDEN. *Med. Klinik*, 1909, No. 41.
- ⁶⁹ BERANECK. *Revue de la Suisse romande*, 1907, No. 6.
- ⁷⁰ YAMANOUCI. *Wiener klin. Wochensch.*, 1908, No. 47.
- ⁷¹ BAUER. *Münch. med. Wochensch.*, 1909, No. 24.
- ⁷² RÖMER. *Brauer's Beiträge zur Klinik der Tuberkulose*, 1908, vol. xi, Section 92.
- ⁷³ WOLFF-EISNER. *Loc. cit.*, pp. 76, 262, 270, 279.
- ⁷⁴ WOLFF-EISNER. *Loc. cit.*, p. 202.
- ⁷⁵ RÖMER. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. xi, p. 98.
- ⁷⁶ VON PIRQUET. "Klin. Studien über Vaccination und Vaccinale Allergie." Wien, Deuticke, 1907.
- ⁷⁷ RÖMER. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. xi, section 2.
- ⁷⁸ HAMBURGER. *Brauer's Beiträge zur Klinik der Tuberkulose*, 1909, vol. xii, section 3. Über Tuberkuloseimmunität.
- ⁷⁹ HAMBURGER. *Loc. cit.*
- ⁸⁰ RÖMER. *Brauer's Beiträge zur Klinik der Tuberkulose*, 1908, vol. xi, section 2, p. 109.
- ⁸¹ FINGER and LANDSTEINER. *Sitzungsberichte der kais. Akademie der Wissenschaften*, Wien, 1906.
- LANDSTEINER. *Zentralblatt für Bakt.*, vol. xli (quoted from Römer in *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. xi, Section 2, p. 96).
- ⁸² BAIL. *Wiener klin. Wochensch.*, 1904, No. 80.
- ⁸³ WOLFF-EISNER. (Quoted from Römer in *Brauer's Beiträge zur Klinik der Tuberkulose*, 1908, vol. xi, Section 2, p. 100.)
- ⁸⁴ RÖMER. *Brauer's Beiträge zur Klinik der Tuberkulose*, *ibid.*
- ⁸⁵ BLOCH. *Med. Klinik*, 1908, No. 51.
- ⁸⁶ VALLÉE and ROSSIGNOL. *Bull. de la Soc. vét. pratique*, March 14, and October, 1906.
- ⁸⁷ WEBER and TITZE. *Arbeiten aus dem kais. Gesundheitsamt*, 1907.
- ⁸⁸ WELEMSKI. (Quoted from Römer in *Brauer's Beiträge zur Klinik der Tuberkulose*, 1908, vol. xi, p. 125).
- ⁸⁹ LÖWENSTEIN. *Zeitsch. für Tuberkulose*, 1905.
- ⁹⁰ MAHMOREK. *Berliner klin. Wochensch.*, 1907, No. 1.
- ⁹¹ KIRALYFI. *Zeitsch. für klin. Med.*, 1909, vol. lxxvii, sections 1 and 2.
- ⁹² BÜECK. *Verhandlungen des internationalen medizinischen Kongresses*, Paris, 1900, vol. ix (Papulosquamöse Tuberculide).
- JADASSOHN. *Kritische Darstellung*; in Ebstein und Schwalbes *Handbuch der prakt. Medizin*.

- ⁹² KLINGEMÜLLER. (Quoted from Wolff-Eisner, *loc. cit.*, p. 130.)
 - ⁹³ RÖMER. *Brauer's Beiträge zur Klinik der Tuberkulose*, 1908, vol. xi, p. 135.
 - ⁹⁴ REID BLAIR. *American Veterinary Review*, vol. xxx, No. 11 (quoted from Römer in *Brauer's Beiträge zur Klinik der Tuberkulose*, 1908, vol. xi, p. 140)
 - ⁹⁵ RÖMER. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. xi.
 - ⁹⁷ WEIBEL. I. A. D., Bern, 1909, "Über die Eiterungs-Koeffizienten der Staphylococcen."
 - ⁹⁸ MORO and DOGANOFF. *Wiener klin. Wochens.*, 1907, No. 31.
 - ⁹⁹ ESCHERICH. *Deutsche med. Wochens.*, 1909, No. 38.
 - ¹⁰⁰ BAUER and ENGEL. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. viii, section 3.
 - ¹⁰¹ MORO. *Deutsche med. Wochens.*, 1909, No. 18.
 - ¹⁰² BAHRDT. *Deutsches Archiv für klin. Med.*, 1908, vol. xciii.
 - ¹⁰³ GRÜNER. *Wiener klin. Wochens.*, 1908, No. 38.
 - ¹⁰⁴ SCHLÄPPER. *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. ix.
 - ¹⁰⁵ BAUER, YAMANOUCHI and BERANECK. *Cf.* p. 138.
 - ¹⁰⁶ MANAUD. *Sem. méd.*, 1909, No. 15, p. 180.
 - ¹⁰⁷ BERANECK. *Revue méd. de la Suisse romande*, 1907, No. 6.
 - ¹⁰⁸ MARMOREK. Quoted from Wolff-Eisner, *loc. cit.*, p. 280.
 - ¹⁰⁹ WOLFF-EISNER. Quoted from Römer, in *Brauer's Beiträge zur Klinik der Tuberkulose*, 1908, vol. xi, p. 129.
 - ¹¹⁰ VON BEHRING. Mentioned in *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. iv.
 - ¹¹¹ BERANECK. *Revue méd. de la Suisse romande*, 1907, No. 6.
 - ¹¹² WOLFF-EISNER. "Frühdiagnose und Tuberkuloseimmunität," 1909, (quoted from Römer in *Brauer's Beiträge zur Klinik der Tuberkulose*, vol. viii, p. 30).
 - ¹¹³ STOCKER. "Über die Erzeugung von Überempfindlichkeit gegen Tuberkulin Beraneck," Stämpfli, Berne, 1911.
 - ¹¹⁴ HEYMANS. *Wiener med. Wochens.*, 1908, No. 25.
 - ¹¹⁵ WOLFF-EISNER. *Loc. cit.*, pp. 266 and 267.
 - ¹¹⁶ RÖMER. *Brauer's Beiträge zur Klinik der Tuberkulose*, 1909, vol. viii, section 1.
 - ¹¹⁷ MORO. *Munch. med. Wochens.*, 1903, Nos. 5 and 39.
 - ¹¹⁸ WOLFF-EISNER. *Loc. cit.*, p. 119.
 - ¹¹⁹ HEYMANS. *Wiener med. Wochens.*, 1908, No. 25.
-

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